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PRECURSORS OF CORPUS CARCINOMA ESTROGENS AND ADENOMATOUS HYPERPLASIA

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STUDY of growth-stimulating substances in relation to the female reproductive tract leads one shortly to a consideration of the role of estrogens in carcinogenesis in these organs. The intense stimulating effect of estrogenic substances on growth of the endometrium is well known, and one can readily understand the logic of investigators who have sought an explanation for abnormal uterine growth in this group of endocrine substances. With the acquisition of knowledge of substances which demonstrated both estrogenic and carcinogenic activity in experimental animals,[1] a fresh impetus entered these investigations. Since that time a great body of knowledge has accumulated concerning the endocrine-tumor relationship. The uterine implications of this work have been ably reviewed at various stages of its development by workers intimately connected with this field: Loeb, 1935;[2] Taylor, 1938;[3] Allen, 1938;[4] Gardner, 1939;[5] Loeb, 1940;[6] Allen, 1940;[7] Greene and Brewer, 1941;[8] Allen, 1942;[9, 10] Taylor, 1944;[11] Nathanson, 1944;[12] and Burrows, 1945.[13]

Study of the evidence for carcinogenic activity of estrogenic substances in experimental animals underscores the importance of species differences and the genetic factor. However, knowledge of this importance of a genetic factor in no manner vitiates the significance of the growth-stimulating activity of estrogens in these animals, and it is a fact that carcinoma of the cervix has been produced in mice by prolonged injection of estrogens. It is an interesting fact that a properly susceptible tissue is needed for this abnormal growth response, but if one accepts the broader concept of the term carcinogenesis, one cannot deny such an activity to the estrogens in certain laboratory animals.

It is perhaps unfortunate for such investigations that the commonly used laboratory animals—rodents and monkeys—rarely develop spontaneous car-

cinoma of the uterus; this would seem to deprive workers in this field of a proper genetic substrate upon which to attempt the provocation of abnormal response by growth-stimulators. Yet much significant work has been done.

Overholser and Allen[4, 15] produced atypical growth in the cervix of monkeys by combining prolonged injection of estrogens with trauma to the cervical epithelium. This abnormal growth response was certainly a form of hyperplasia rather than carcinoma, but it did resemble certain borderline cervical lesions which we are now learning to recognize in the human being. Engle and Smith[16] and Zuckerman[17] also reported failure to obtain uterine carcinoma in monkeys by long-term estrogenic stimulation. In the years 1934 to 1939, a variety of atypical growths were reported following estrogen injection, but certainly few of these could be definitely classified as cancer, and still fewer significantly related to spontaneous human tumors[18-24] Lacassagne[19] described rather active squamous metaplasia in the uterus of a mouse treated with estrone. This tissue contained numerous mitotic figures and invasion of the submucosa at one point, but no metastases. Perry and Ginzton[23] reported the production of uterine carcinoma in a few mice of a group which had received both theelin and 1:2:5:6 dibenzanthracene.

The studies of Allen, Gardner, and their co-workers were finally fruitful in producing true carcinoma of the cervix in mice by prolonged estrogen stimulation.[25-28] In 1938 they reported eighteen invasive cervical tumors produced in mice; these tumors metastasized to lymph nodes and could be transplanted to several generations of hosts. In 1941 and 1942 they reported significant numbers of cervical carcinomas produced in hybrid mice by chronic estrogen therapy. Miller and Pybus[29] reported similar results in 1942.

Thus a notable accomplishment had been attained: the production of malignant uterine neoplasms with estrogens in rodents, ordinarily resistent to the spontaneous growth of such tumors.

The reports of Burrows[30] and Greene[31] concerning spontaneous adenocarcinoma of the endometrium in rabbits must also be regarded as significant. Both these workers encountered evidence elsewhere in the body suggesting an endocrinopathy in these tumor-bearing animals. Greene described preceding toxemia and liver damage with a period of infertility and "cystic endometritis" leading up to tumor formation and he interpreted these findings as evidence of abnormality in the pattern of internal secretions. Naturally in speculation about abnormal growth patterns in these animals one is attracted to implication of the estrogens.

Since species differences evidently are of considerable significance in the study of abnormal growth of the endometrium, evidence of an endocrine-tumor relationship in the human being is important. We have studied this problem clinically and histologically in respect to abnormal endometrial growth, and wish to present data in the following categories: (a) the stimulating effects of functioning ovarian tumors; (b) hyperplasia of the human endometrium following prolonged estrogen administration; (c) adenocarcinoma of the human endometrium following prolonged estrogen stimulation; (d) relation of hyperplasia of the endometrium to the development of adenocarcinoma.

(A) *Response of the Human Endometrium to Granulosa Cell Tumor of the Ovary.*—A natural, if uncontrolled, experiment in prolonged estrogen stimula-

tion of the post menopausal human uterus is set up in the patient who develops a granulosa cell (or theca cell) tumor of the ovary: these patients are frequently advanced in years, the estrogen stimulation is prolonged, and it lacks rhythmicity or interruption, for there is no regular corpus luteum formation to modify the constant estrogenic effect. The finding of hyperplasia of the endometrium in patients harboring such an ovarian tumor is well known. If prolonged unopposed estrogen stimulation can produce endometrial carcinoma in individuals of such an age group,[32] one would expect a significant percentage of those patients—if they possess the proper genetic background to make them cancer susceptible—to respond with endometrial malignancy. There have been increasing reports in the recent literature pointing to the fulfillment of this expectation. Many authors have submitted reports increasing the impression of a relatively high incidence of corpus carcinoma associated with granulosa or theca cell tumors of the ovary.[33-45] Especially noteworthy is the experience at the Mayo Clinic reported by Hodgson, Dockerty, and Mussey,[43] who found that in a group of thirty-eight postmenopausal patients with granulosa cell tumors,

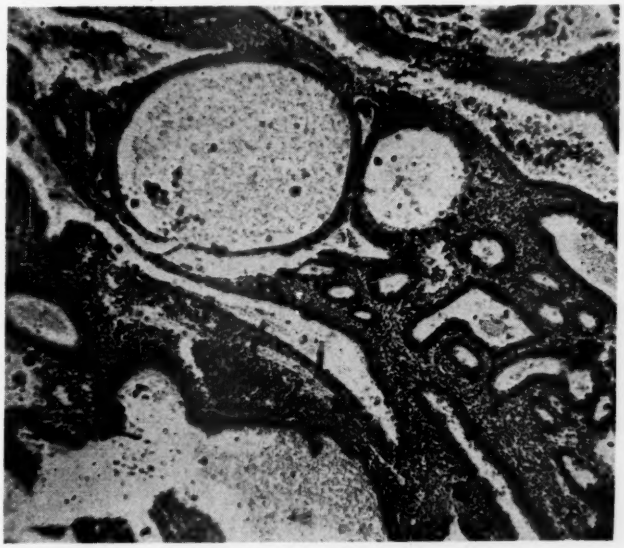

Fig. 1.—(×250) Fully developed cystic glandular hyperplasia.

eight, or 21 per cent, had accompanying corpus carcinoma; three also developed carcinoma of the breast. The experience at the Free Hospital for Women is comparable, for Pemberton[44] reported seven cases of corpus carcinoma which had developed in patients with functioning ovarian tumors, and Hertig[45] states that at least 18 to 20 per cent of the patients with granulosa cell or theca cell tumors of the ovary have associated carcinoma of the corpus.

The group of granulosa cell and theca cell tumors in our laboratory is small. Of nine patients with such functioning ovarian tumors, we have found only one with an associated endometrial carcinoma. We have studied the endometrium in each of these postmenopausal cases, however, and we have noted a striking degree of hyperplasia in many. Some are simply examples of fully

developed cystic glandular hyperplasia, but others show greater activity, with papillary buds in the glands, extreme crowding of glands, heaping up of the epithelium, and sometimes more eosinophilic staining—all qualities which we have noted in endometria stimulated by exogenous estrogens. One can place these hyperplastic endometria in a graded progression of activity which moves quite readily toward the malignant one (Figs. 1 to 7).

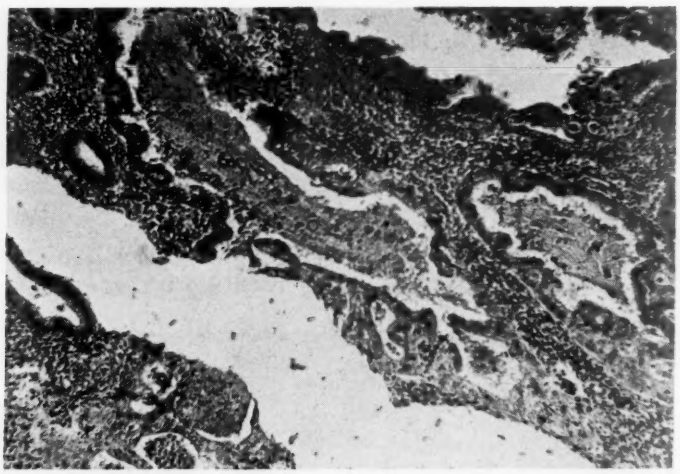

Fig. 2.—(×240) Pale staining glands with mildly papillary pattern.

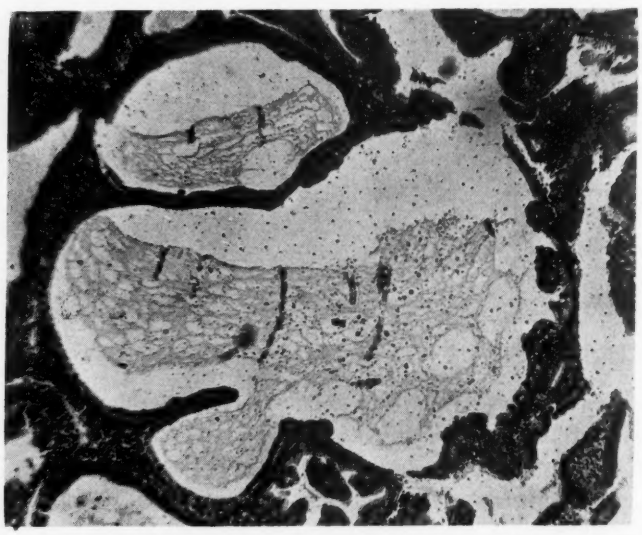

Fig. 3.—(×210) Intraglandular budding scattered through endometrium which otherwise shows ordinary hyperplastic pattern.

This accumulating evidence of the association of estrogen-producing ovarian tumors with corpus carcinoma together with data obtained from study of the pattern of adenomatous hyperplasia produced in such cases are certainly suggestive of an estrogen-cancer relationship.

(B) *Hyperplasia of the Human Endometrium Following Prolonged Estrogen Administration.*—Another human experiment has been set up in recent years by the widespread administration of estrogens to postomenopausal women. The relatively low cost of stilbestrol and the ease of its administration have made its general use promiscuous. Uterine bleeding provoked in postmenopausal patients by this medication has become such a commonplace occurrence

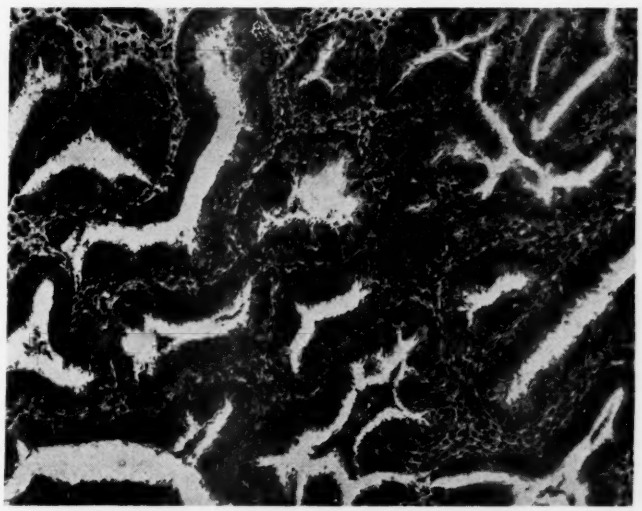

Fig. 4.—(×320) Area of crowded hyperplastic glands, with pseudostratification.

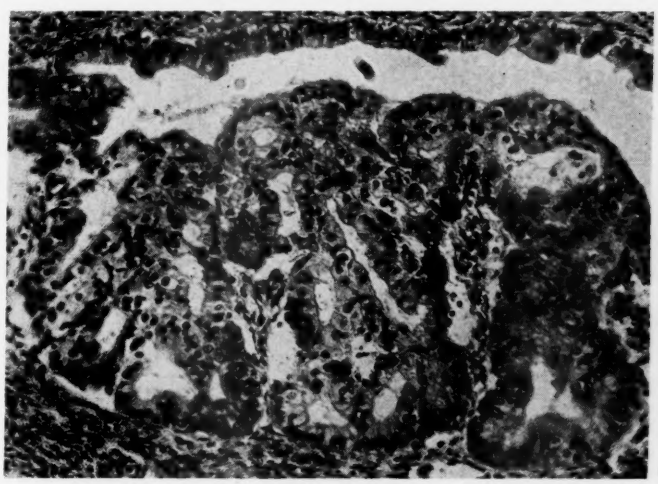

Fig. 5.—(×400) Adenomatous focus in hyperplastic endometrium.

that an idiomatic expression "stilbestrol bleeding" has found use on our gynecologic service when these cases are admitted for the necessary diagnostic curettage. We have not noted exceptional stimulating qualities in stilbestrol differing from those of other estrogenic substances, and the above-described frequent bleeding sequence is probably a mere reflection of its ease of administration, low cost and relative potency, and, therefore, of its frequent use.

We have studied twenty human endometria with advanced degrees of hyperplasia produced by prolonged estrogen administration, and once again noted qualities which recurred with considerable frequency in the more active-appearing tissues: crowding of the glands into a lawless pattern, heaping up of the epithelium into pseudostratified masses, at times accompanied by intraglandular

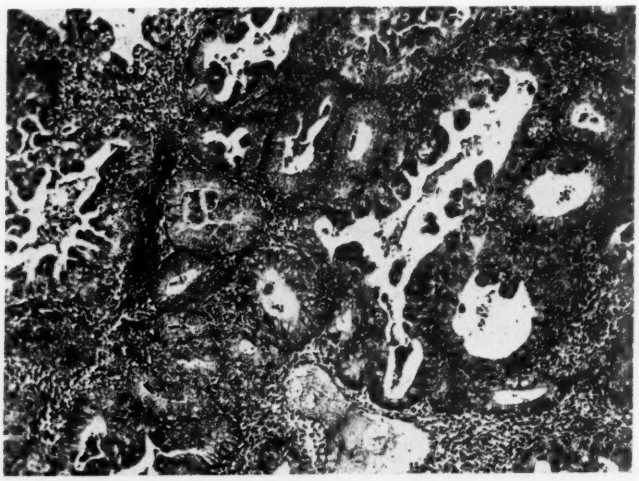

Fig. 6.—(×250) Papillary budding pattern of intense hyperplastic activity.

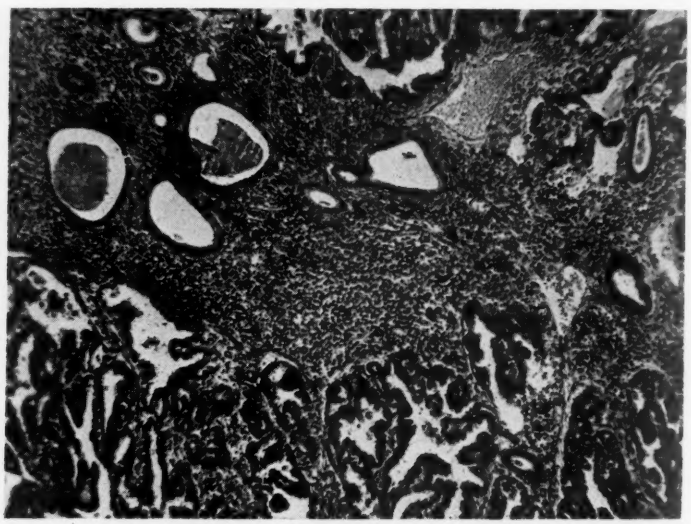

Fig. 7.—(×250) Papillary—appearing adenocarcinoma interspersed with areas of cystic glandular hyperplasia.

budding simulating a papillary pattern, paler, sometimes eosinophilic staining epithelium, and occasionally syncitiumlike epithelial masses on the surface; these metaplastic (adenomatous) areas are frequently focal. The accompanying microphotographs (Figs. 8 to 16) are examples of such activity in tissues from postmenopausal patients who have received prolonged medication with estrogens. We have not found this response to be related to the quantity of

the drug administered either in individual or total dosage, but rather to the persistent stimulus. None of these endometria could be called malignant, but all appeared very active, and some varied sufficiently from the well-known pattern of cystic glandular hyperplasia as to convince both pathologist and clinician that the patient's interests would best be served by prophylactic hysterectomy.

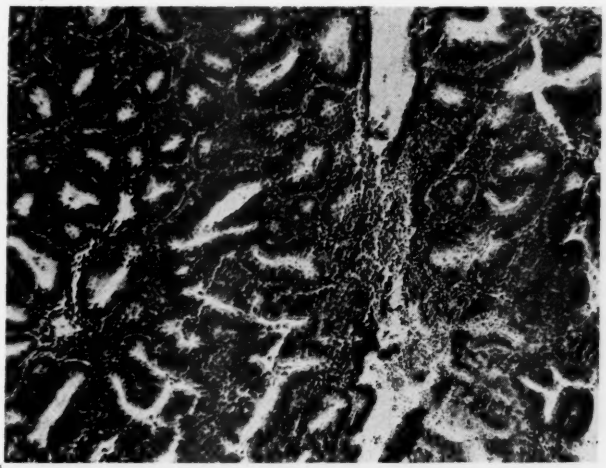

Fig. 8.—(×275) Crowding of glands in intensely hyperplastic endometrium.

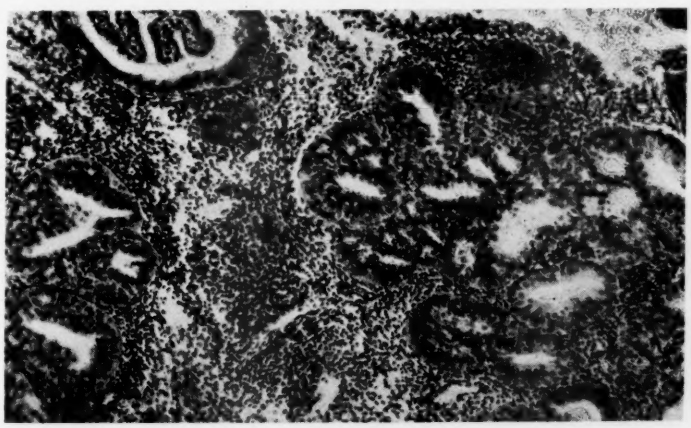

Fig. 9.—(×320) Adenoma-like foci of crowded glands with pseudostratification.

It is important to point out that any presentation of a general endometrial patern by a single microphotograph must necessarily be incomplete; Figs. 8 to 16 have been chosen in an effort to present an integrated picture of this process.

It is interesting to note the characteristics which these endometria share with those produced by the stimulus of granulosa cell tumors.

(C) *Adenocarcinoma of the Human Endometrium Following Prolonged Estrogen Administration*:—There have been occasional suggestions in recent years that spontaneous corpus carcinoma in human beings may be related eti-

ologically to estrogen stimulation.[46-49] Smith[47] noted frequent stromal or theca cell activity in the ovaries of patients operated upon for corpus carcinoma. More recently Ayre and Bauld[49] reported evidence of thiamine deficiency in such patients, and they postulated resulting liver damage, failure of estrogen conjugation, and thus resultant high level of endogenous estrogen.

In spite of the common use of hormonal therapy for menopausal symptoms in recent years, there have been few reports of resultant uterine carcinoma.

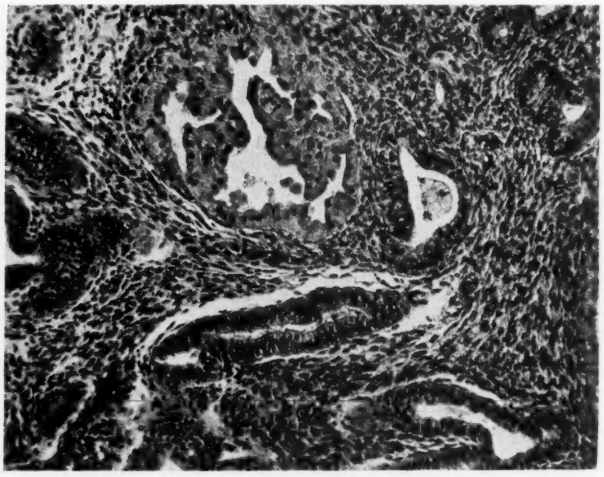

Fig. 10.—(×360) Eosinophilic staining gland with intraluminal budding.

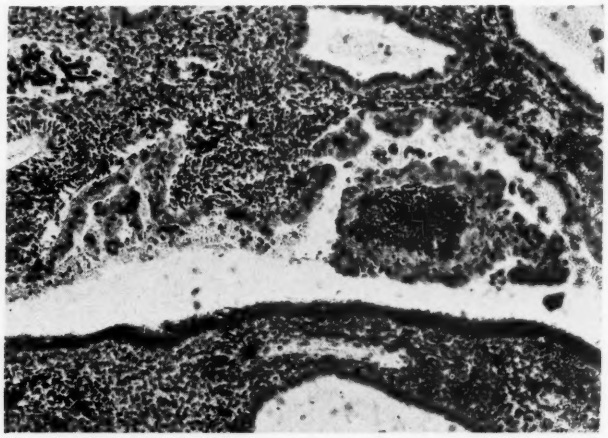

Fig. 11.—(×320) Early budding in focus of pale glands.

Gemell and Jeffcoate[50] reported three cervical carcinomas arising in a group of forty-three patients who had received estrogen therapy for senile vaginitis, but study of these histories suggests the probability that these lesions were present prior to the onset of treatment. Henry,[51] in 1945, described two cases of marked endometrial hyperplasia following stilbestrol therapy whose pattern suggested malignancy and he stressed the importance of the persistent stimu-

lus rather than quantity of dosage. Fremont-Smith, Meigs, Graham, and Gilbert,[52] in 1946, reported the development of undoubted corpus carcinoma in a patient who had received estrogenic therapy over a long period of time; the history of this case certainly casts strong suspicion on this medication as an etiologic factor. It is well known that many experienced workers in the endocrine field have denied that estrogens possess carcinogenic properties in the human. Some have pointed to the widespread use of estrogens and the lack of precise evidence that malignancy has been produced by such administration.[53, 54]

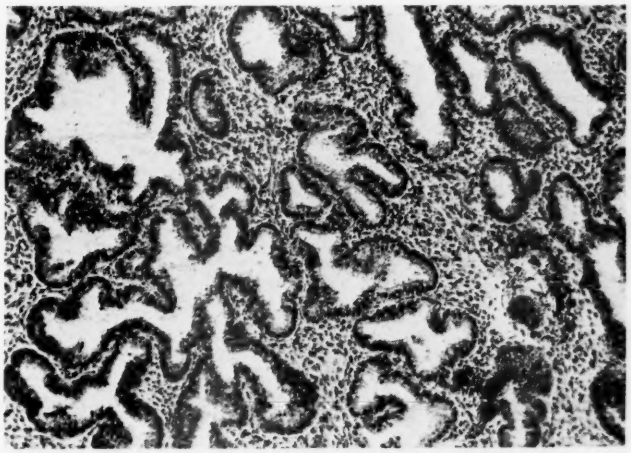

Fig. 12.—(×250) Scattered areas of adenomatous hyperplasia.

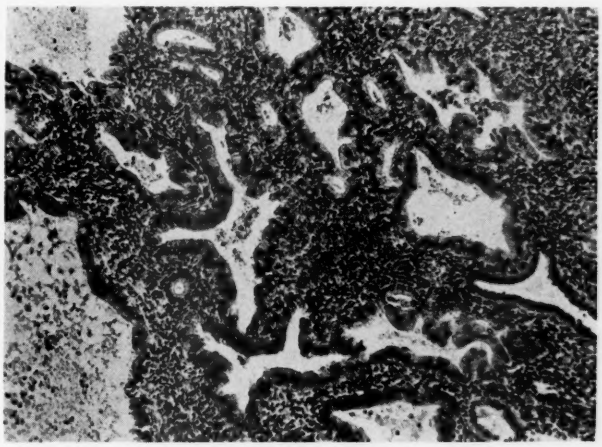

Fig. 13.—(×300) Early intraluminal budding in occasional adenomatous areas.

In this connection it is important to bear in mind the probable importance of the genetic factor in creating tissue susceptibility to abnormal growth stimuli, so that one should not expect more than an occasional union of the proper "substrate" and the proper stimulus in any general group of patients.

Group I

We have studied five patients who have developed adenocarcinoma of the corpus uteri following prolonged estrogen administration. It is impossible to achieve proper controls in such a clinical investigation; it is therefore possible to dispute the relationship between the medication and the neoplasm in any individual case, in view of the well-known character of this tumor in remaining local for relatively long periods of time. However, these histories are extremely suggestive of an etiologic relationship, and the histologic data sup-

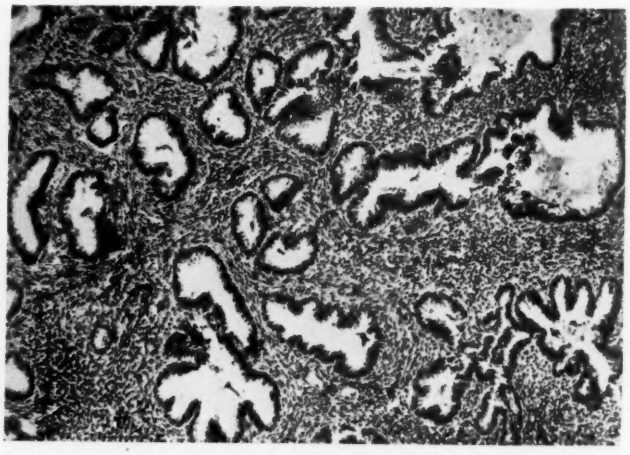

Fig. 14.—(×275) Adenomatous hyperplasia fairly uniform.

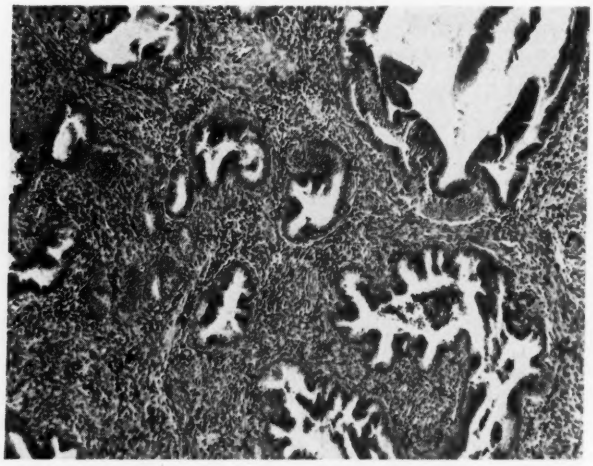

Fig. 15.—(×260) Adenomatous hyperplasia with areas of intense activity.

porting them are also of a pattern which makes the suggestion strong enough to be signficant and certainly to warrant further study. Brief abstracts of these cases are presented below.

Case 1.—G. K., aged 56 years. In 1938, at the age of 48 years, radiation castration with x-ray therapy for menopausal bleeding was administered. Pelvic examination at that time was negative; no curettage

was performed; no bleeding occurred following therapy. In May, 1941, a parathyroid adenoma was discovered and removed. In November, 1941, postmenopausal osteoporosis was diagnosed, and treatment with estradiol started in six-week courses followed by two weeks of rest. In March, 1942, estradiol was stopped and the patient was started on 1 milligram of stilbestrol daily for twenty-four days of each month; this therapeutic regime was continued for the next two years. In February, 1944, the dose was cut to 0.5 milligram because the patient had noted a monthly episode of bleeding.

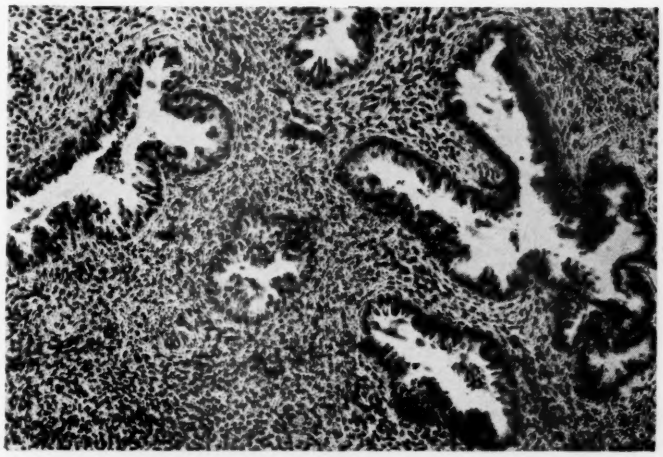

Fig. 16.—(×360) Adenomatous hyperplasia.

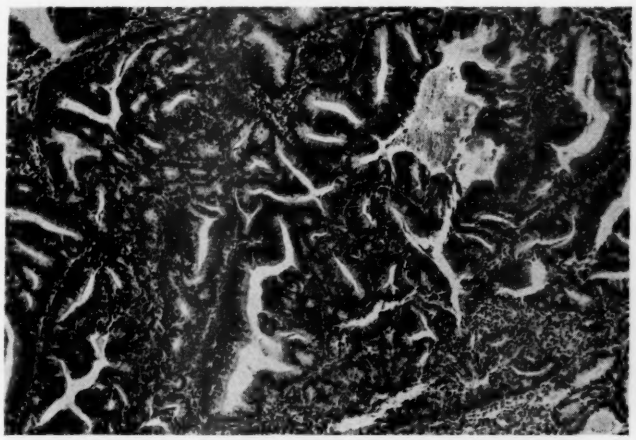

Fig. 17.—(×260) Adenocarcinoma with budding mildly papillary pattern.

This withdrawal type of bleeding continued for the next several months until a curettage was performed in June, 1944. Sections of these curettings and those of the subsequent hysterectomy specimen revealed adenocarcinoma of the corpus uteri. Fig. 17 illustrates a characteristic area of this malignant endometrial tumor.

Case 2.—S. S., aged 50 years. In 1934, at the age of 40 years, this patient came under gynecologic supervision for amenorrhea. She received intermittent injections of estrogenic substances during the next seven years because of vary-

ing periods of amenorrhea and recurring menopausal symptoms. In December, 1941, at the age of 47 years, the menses ceased and the patient took almost daily stilbestrol for the next three years. In November, 1944, a curettage was performed because of onset of a blood-tinged vaginal discharge, and this revealed adenocarcinoma of the corpus uteri, as did sections of the subsequently removed uterus (Fig. 18).

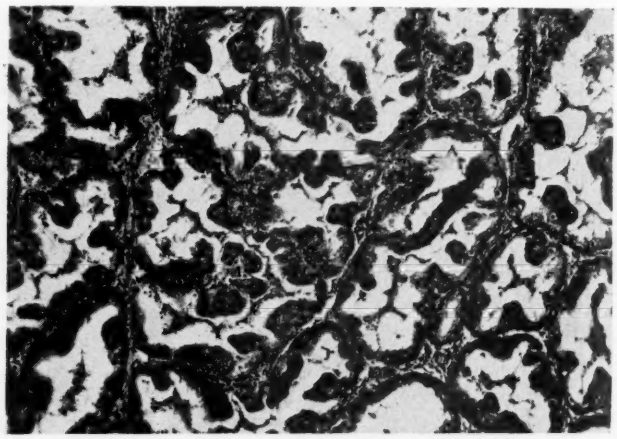

Fig. 18.—(×310) Fully developed budding which gives tissue papillary appearance.

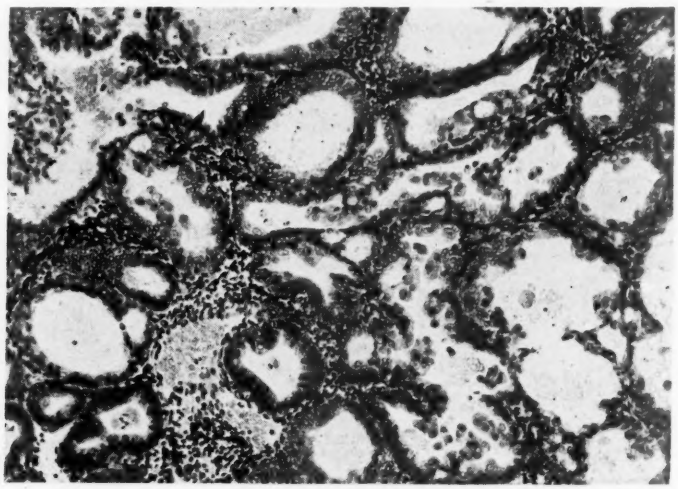

Fig. 19.—(×310) Adenocarcinoma with budding pattern.

CASE 3.—E. B., aged 56 years. This patient is especially interesting in that her past history included an abdominoperineal resection for carcinoma of the rectum. An uneventful menopause occurred in 1939, seven years prior to her present admission. During this seven-year interval, the patient was treated constantly with estrogens for menopausal symptoms, and in recent years she had been taking almost daily stilbestrol.

She was admitted to the hospital in 1946 because of local recurrence of the rectal neoplasm, and vaginal bleeding. Curettage revealed a distinct, primary

adenocarcinoma of the corpus, unrelated histologically to the rectal tumor. Fig. 19 illustrates the characteristic pattern of this endometrial neoplasm.

CASE 4.—M. W., aged 60 years. A spontaneous uneventful menopause occurred in this patient at the age of 48 years. This was notable only in that the patient received a course of radiation therapy to her thyroid for hyperthyroidism. For three years following the cessation of her menses, she received estrogenic therapy for menopausal symptoms. During the succeeding six years no hormonal treatment was given, then, at the age of 57 years, her physician resumed estrogenic and vitamin therapy. This was continued for three years, during which time she noted intermittent stimulation of her breasts.

In 1946, at the age of 60 years, a curettage was performed because of the onset of slight vaginal bleeding, and this revealed a typical adenocarcinoma of the uterine corpus (Fig. 20).

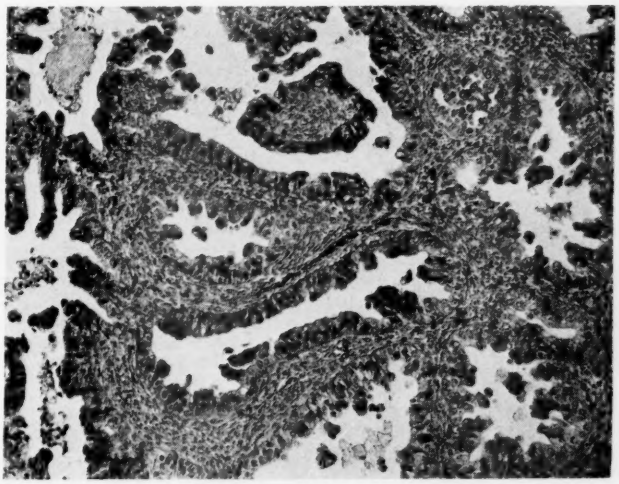

Fig. 20.—(×260) Adenocarcinoma with focal appearance of intense adenomatous hyperplasia.

CASE 5.—S. M., aged 41 years. This patient first came under gynecologic supervision in 1932 when she consulted her physician for amenorrhea of approximately one year's duration. She was then 34 years old. During the succeeding three years, she received intensive estrogenic therapy, with periods of rest and the occasional addition of progesterone. She continued to have long periods of amenorrhea, though there were intermittent scant menses hardly more than spotting. Occasional endometrial biopsies were taken; they revealed normal endometrium without secretory change. In 1936 and 1937, she received little endocrine therapy, but in 1938 this was resumed: it was not given regularly throughout this year; emphasis was placed on progesterone. From May to September, 1938, menses were fairly regular, but irregular spotting recurred thereafter. In March, 1939, significant noncyclic bleeding occurred, and a curettage was performed; this revealed endometrial hyperplasia and metaplasia, and areas which were interpreted as malignant. Because of the clinical impression that the atypical endometrial pattern represented an endocrine effect rather than malignancy, no further treatment was offered until September, 1939. At that time repeat curettage demonstrated adenocarcinoma beyond any reasonable doubt, and a complete hysterectomy and bilateral salpingo-oöphorectomy

were performed (Figs. 21 and 22). The surgical specimen not only confirmed the diagnosis of malignancy of the endometrium, but also contained metastatic disease in both ovaries.

The histologic pattern of these malignant endometria developing in patients who had received prolonged estrogen therapy is most interesting in that it bears considerable resemblance to the hyperplastic and metaplastic endometria described above. In some areas one gains the impression that this process is but an intensification of an atypical adenomatous pattern of hyperplasia. One can

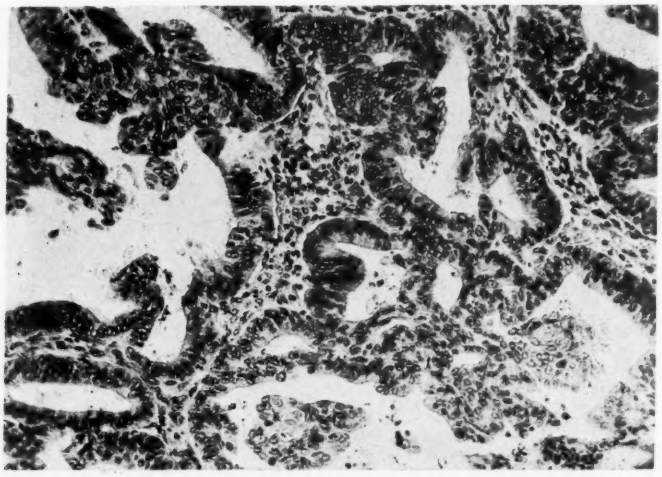

Fig. 21.—(×300) Adenocarcinoma with papillary qualities.

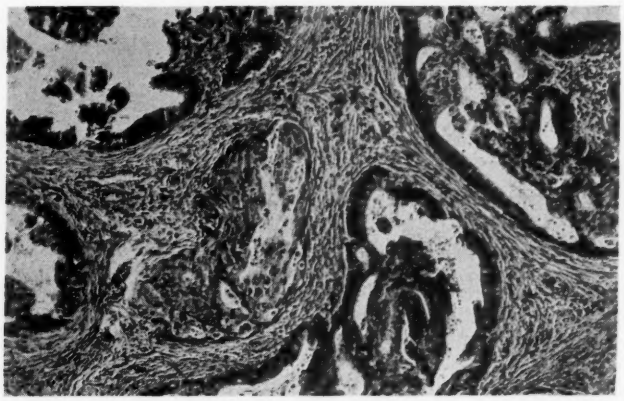

Fig. 22.—(×360) Papillary, budding glandular foci, some with pale staining qualities.

see typical cystic glandular hyperplasia, atypical (metaplastic) hyperplasia, and adenocarcinoma side by side in some sections. The multifocal malignant processes, often separated by areas of typical hyperplasia, present the picture of a generally stimulated tissue which has responded more intensely in some areas. There is a characteristic pattern which constantly recurs through these tissues; it is almost papillary in form; it shares morphologic properties with other tissues known to have been stimulated by estrogens.

Group II

We have also studied three other corpus carcinomas and an ovarian adenocarcinoma whose development may have been accelerated by estrogen administration and their histologic pattern modified. They are important because endocrine therapy obscured or delayed diagnosis; there is no significant evidence in these cases that the administered estrogenic substances initiated the abnormal endometrial growth. Resemblance of these tissues to each other, however, and to the patterns described above, lends the impression that the endocrines may have modified them.

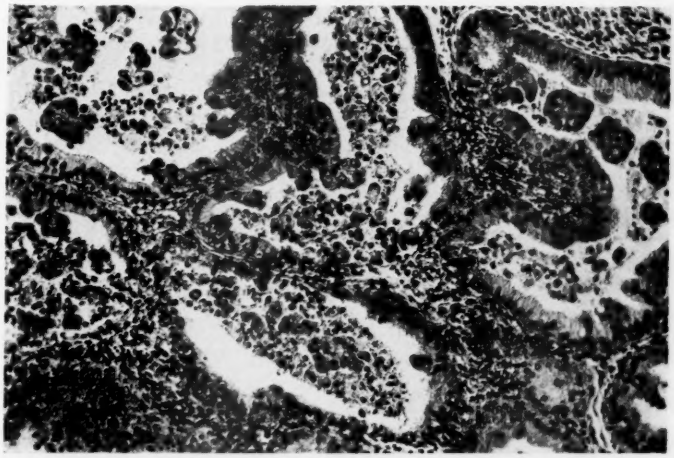

Fig. 23.—(×400) Budding pattern of intense hyperplastic activity in crowded glands.

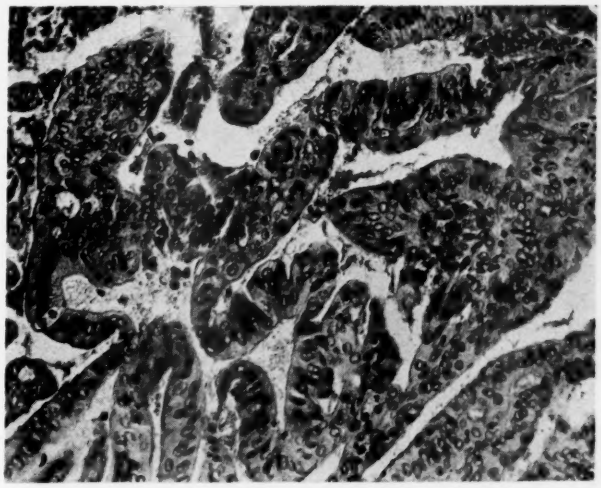

Fig. 24.—(×400) Localized area of well differentiated adenocarcinoma.

Case 6.—F. Y., aged 30 years. This patient presented a six-year history of sterility, repeated episodes of profuse bleeding, and varying courses of endocrine therapy. Curettage had been performed on three occasions before her final treatment; the last of these, three years before final admission, revealed

hyperplasia of the endometrium. At the age of 30 years, another episode of profuse vaginal bleeding brought the patient into our hospital, where curettage revealed markedly hyperplastic endometrium with metaplastic areas (Fig. 23). Because of the intense picture of activity in this endometrium, and because her repeated blood loss was incapacitating, a hysterectomy was advised. Study of the hysterectomy specimen revealed markedly active hyperplasia, and also localized areas of adenocarcinoma (Fig. 24).

CASE 7.—A. C., aged 38 years. This patient came under observation in 1936 at the age of 32 years because of enormous obesity, sterility, and long-standing irregular menses. There were frequent episodes of amenorrhea followed by persistent bleeding. In 1936 and 1937, the patient received prolonged estrogenic therapy, but in 1938 and 1939, there was no significant endocrine medication. Following weight reduction, normal menses were resumed in 1939 and continued in 1940 and 1941; infrequent estrogen, corpus luteum, or thyroid preparations were offered. After seven months of normal menstrual cycles menorrhagia was resumed in April, 1942, and curettage in June revealed adenocarcinoma of the corpus (Fig. 25).

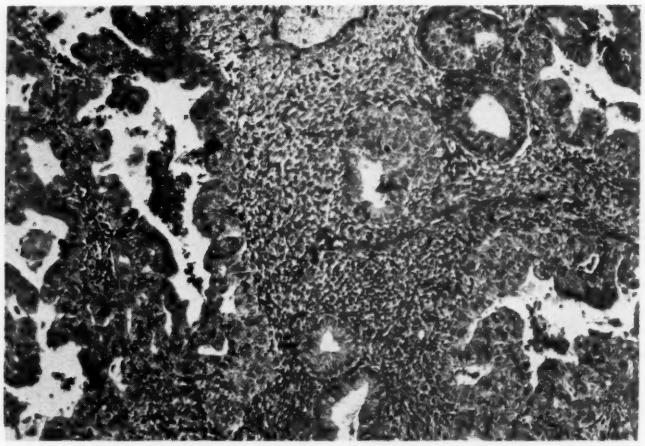

Fig. 25.—(×275) Adenocarcinoma with papillary budding foci.

CASE 8.—T. L., aged 45 years. This patient sought gynecologic care for vaginal discharge of three months' duration, five years after a normal menopause. From January to May, 1937, estrogenic therapy was given for senile vaginitis; irregular staining of a withdrawal type was noted. This inconstant spotting continued from June to October, in spite of discontinuation of therapy, and curettage in October revealed adenocarcinoma of the corpus (Fig. 26).

CASE 9.—G. J., aged 41 years, entered gynecologic supervision in September, 1940, at the age of 40 years, approximately one year after a normal menopause. Pelvic examination revealed no abnormality. Stilbestrol therapy for menopausal symptoms was started and it was continued through October, November, and December of that year. After a four-week interval of rest, it was resumed in January, 1941. In February, the patient complained of lower abdominal pain; examination revealed a large cystic mass filling the cul-de-sac. Laparotomy was performed and hysterectomy with bilateral salpingo-oöphorectomy readily accomplished. Pathologic study revealed endometriosis of the right ovary with adenocarcinoma probably arising from an endometrial cyst (Fig. 27).

(D) *Relation of Hyperplasia of the Endometrium to the Development of Corpus Carcinoma.*—It has been well established that persistent unopposed estrogenic stimulation of the endometrium is responsible for the production of the characteristic pattern of cystic glandular hyperplasia. A possible relation between this hyperplasia and adenocarcinoma of the endometrium has been sought for some time without general agreement concerning the interpretation of data or conclusions submitted. There have been recurrent reports of corpus carcinoma developing in patients with coexistent or prior hyperplasia.[55-61]

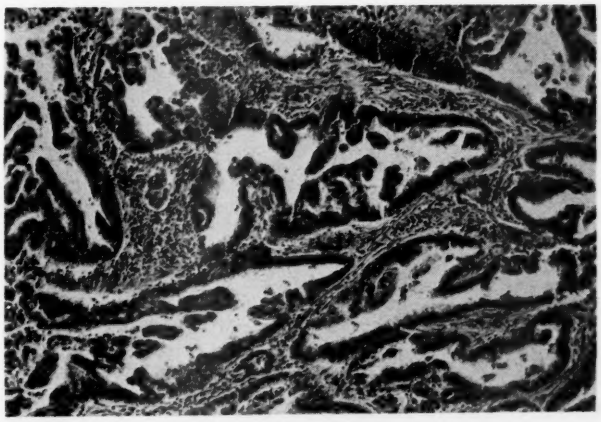

Fig. 26.—(×300) Adenocarcinoma with papillary pattern.

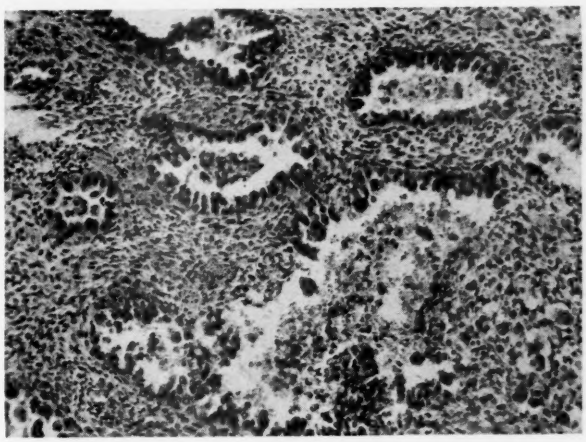

Fig. 27.—(×275) Papillary adenocarcinoma of ovary with endometrial pattern.

Taylor, in 1932,[62] and Novak and Yui, in 1936,[63] reported their studies of this problem, and they concluded that there was a developmental relationship between endometrial hyperplasia and carcinoma. The latter authors emphasized the importance of hyperplasias persisting into the postmenopausal age group; they described atypical patterns of hyperplasia of a type which we have noted in patients who have continued to the full evolution of neoplasm, and which we have also seen in endometria stimulated by administered estrogens (see above).

Herrell, in 1939,[46] described "persistent proliferative endometrium" as a frequent accompaniment of corpus carcinoma, but did not designate this pattern as a hyperplastic one. It is apparent, however, that his studies suggested a picture of estrogenic endometrial stimulation, for they led him to the conclusion that estrogens played an etiologic role in the development of endometrial carcinoma.

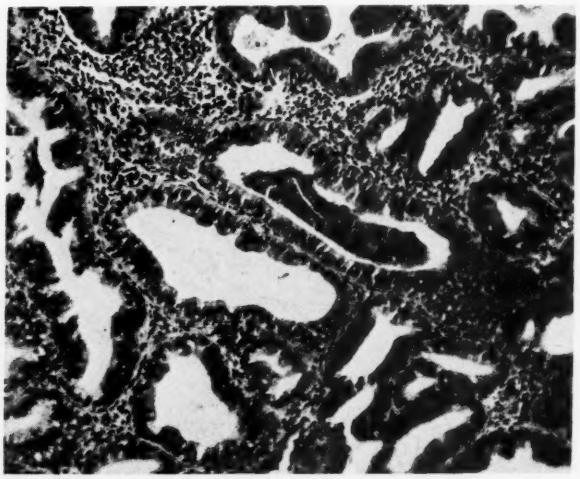

Fig. 28.—(×360) Adenomatous focus of crowded glands.

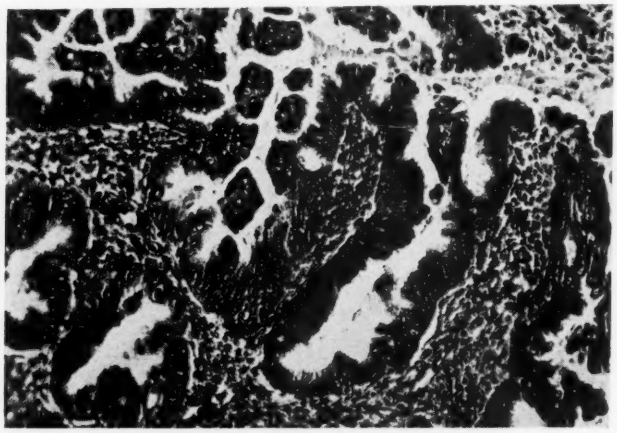

Fig. 29.—(×380) Papillary budding pattern of glands.

Others have doubted the importance of endometrial hyperplasia in the development of corpus carcinoma.[64-67] Mack, in 1929,[68] and Hintze, in that same year,[69] reported follow-up studies of patients with endometrial hyperplasia with few examples of later carcinoma.

In an effort to evaluate the endocrine background of patients with corpus carcinoma, we have studied their reproductive histories, and we have noted deviations which suggest abnormality of internal secretions: an increased incidence of infertility, delayed menopause, and menopausal bleeding.[70] The

latter observations have also been reported by Crossen and Hobbs,[71] and Randall[72] in their clinical investigations of adenocarcinoma of the corpus.

Another study in our clinic investigating the nature of the menopause in relation to subsequent carcinoma[73] also suggested an endocrine factor. It revealed that among women who had been treated radiotherapeutically for benign causes of bleeding at the menopause, there were observed three and one-half

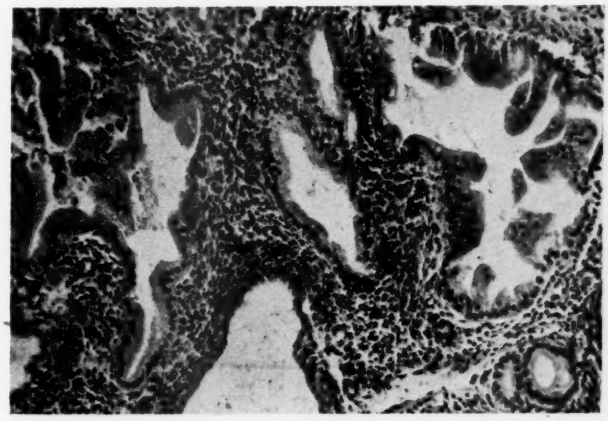

Fig. 30.—(×380) Focus of pale staining, budding glands.

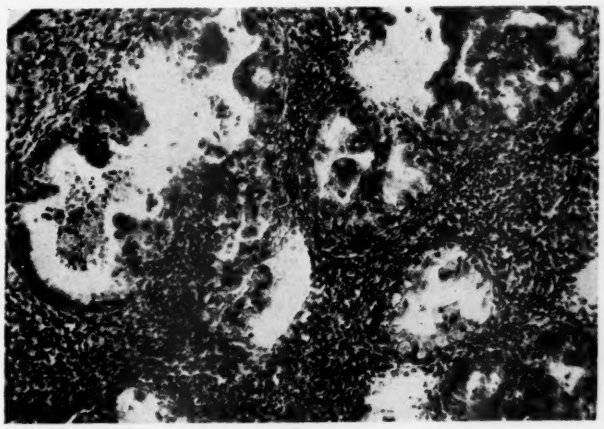

Fig. 31.—(×360) Adenomatous focus in a generally hyperplastic endometrium.

times as many subsequent corpus carcinomas as would be expected in a similar sampling of the general population. In surveying the endometria obtained from individuals who have required treatment for benign causes of bleeding at the menopause, we have noted hyperplasia in 31 per cent. It would appear that repeat curettage at varying stages of the bleeding episodes might increase this proportion of hyperplasia, for there may be irregular shedding of this tissue.[74] At any rate, the number that showed progesterone influence was small (13 per cent). There is some evidence to suggest that these menopausal patterns may persist asymptomatically into the postmenopausal period.[75, 76]

Thus, these individuals who apparently have an increased susceptibility to the later development of corpus carcinoma demonstrate a significant frequency of endocrine stigmata of a type which has been associated with infrequent ovulation, and probably noncyclic persistent unopposed estrogen stimulation.

Certainly every laboratory of gynecologic pathology frequently encounters hyperplastic endometria which suggest a stage in the development of carcinoma;

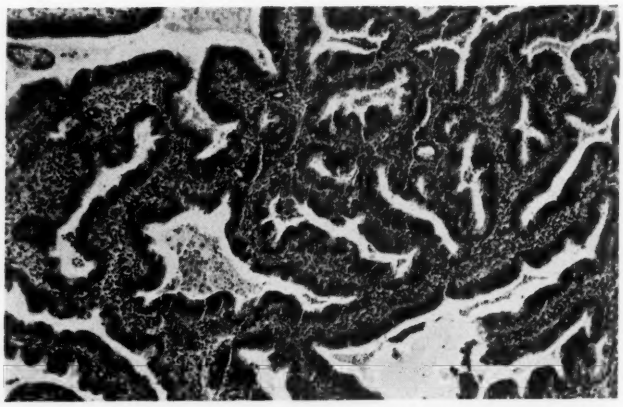

Fig. 32.—(×250) Adenomalike area of crowded glands.

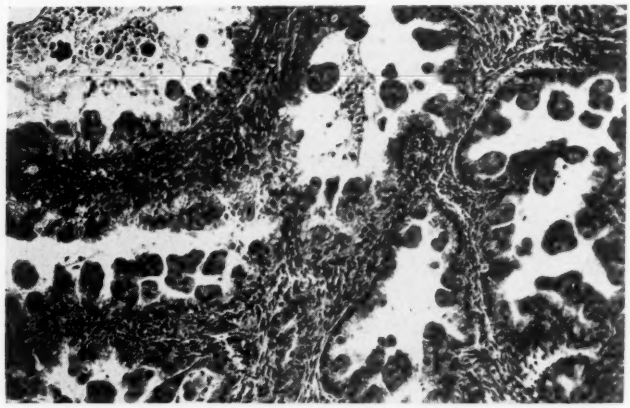

Fig. 33.—(×360) Budding papillary glandular pattern.

in some instances one can observe areas of cystic glandular hyperplasia surrounding a true endometrial adenocarcinoma. We wish to call attention to the pattern of atypical (adenomatous) hyperplasia which is sometimes encountered in patients who have suffered repeated episodes of "functional bleeding" (Figs. 28 and 29): it is a papillary pattern of glandular activity, of an identical nature to that which has been described above as an end result of endogenous (functioning ovarian tumors) or exogenous (estrogen therapy) estrogen stimulation. The histologic picture in some of these cases is very difficult to distinguish from frank adenocarcinoma. Furthermore, it is interesting to note that in some patients with repeated episodes of bleeding who have progressed to the development of true adenocarcinoma, the pattern of the pre-existing hyperplasia is a

similar one to that described above with focal metaplastic areas (Figs. 30, 31, 32, and 33). In some cases one can distinguish several stages of apparent development of the neoplasm in the same endometrium (Fig. 34). These histologic considerations suggest to us the probability that there does exist a type of endometrial hyperplasia which can progress to adenocarcinoma under suitable conditions.

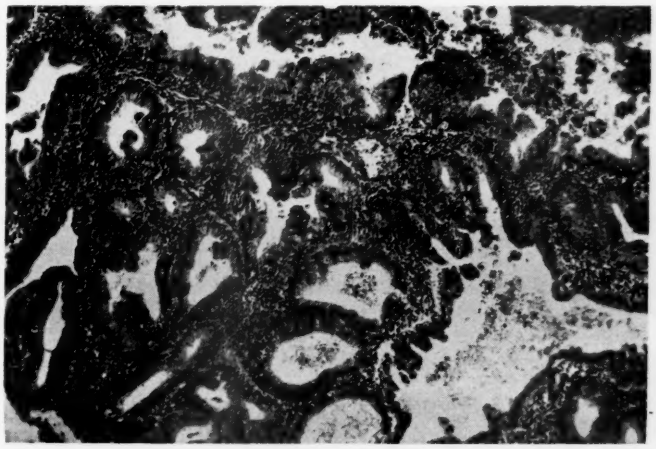

Fig. 34.—(×275) Foci of adenomatous hyperplasia of varying intensity.

Summary and Conclusions

1. A pattern of adenomatous hyperplasia of the endometrium is described which bears a constant relation to estrogen stimulation in both benign and malignant tissues.

2. We have presented data concerning this endocrine-tumor relationship in four related groups: (a) Endometrial hyperplasia produced by granulosa cell tumors. (b) Endometrial hyperplasia produced by prolonged estrogen administration. (c) Endometrial adenocarcinoma arising in patients receiving prolonged estrogen administration. (d) Endometrial patterns in patients with recurrent episodes of "functional bleeding."

3. The well-defined histologic pattern recurring in these related groups of tissues suggests that endogenous or exogenous estrogens play a role in the development of corpus carcinoma. We have called attention to a type of endometrial hyperplasia which is a cancer precursor.

The author wishes to express his gratitude to his associates of the Staff of the Sloane Hospital, to Dr. Homer Kesten of the Department of Pathology, and to Dr. Earl Engle of the Department of Anatomy, College of Physicians and Surgeons of Columbia University, for their aid in this study. They have given generously of their time and material.

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FATAL ECLAMPSIA

A Clinical and Anatomic Correlative Study

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THIS paper represents a summary of all fatal cases of eclampsia which were examined at autopsy in the Department of Pathology, Duke Hospital, during the period 1930 to 1946. Although primary emphasis has been placed upon the pathologic aspects of these cases, it is believed that a correlation of the clinical history and the postmortem findings may prove most useful in adducing conclusions of significance to both clinician and pathologist.

During this period there were 33 necropsies performed in cases of fatal eclampsia. Our criteria for determination of eclampsia were the appearance of the usual signs of severe toxemia in a gravid patient during the latter half of her gestation, together with a generalized motor seizure. It is true that eight of these patients never had convulsions even up to their exitus.* The adjudgment of these eight cases as eclampsia depended upon the finding of focal hyaline or fibrinoid necrosis in the liver with a history of severe toxemia. Therefore the criteria for classification in this category are the following: (1) severe toxemia with generalized motor seizure during life in the last half of pregnancy, or (2) severe toxemia resulting in death, autopsy revealing focal hyaline hepatic necroses.

The occurrence of convulsions in pregnancy and especially in toxemia has been well discussed by Burnett.[4] He expresses the thought that, with identical degrees of albuminuria, elevation of blood pressure, and other signs of toxemia, one patient will present eclamptic convulsions, while another will not. It is his opinion, therefore, that a varying degree of nervous instability exists which plays a part in causing the eclamptic fit.

This is in keeping with the concept that for a generalized motor discharge of the central nervous system there exists a very definite threshold as in any other physiologic or pathophysiologic process in the body. This threshold varies, so that what may be adequate stimuli in one patient with toxemia may fall short of the threshold in another.

Clinical Analysis

A great number of reports appear in the literature concerning the vital statistics on eclampsia.[5, 6] As might be expected with such a small series as this, there are percentage variations from those reports which draw upon hundreds of nonfatal cases. Therefore it is doubtful that the differences are significant.

*This occurrence has been described by many authors.[1-3]

The age range was 13 to 41 years, with a mean of 24.1 years. Eighty per cent of the patients lie within the range of 15 to 30 years. As might be expected, the average age of the primiparous patient was considerably less than that of those who had had previous pregnancies: 19.7 years, as compared with 29 years. This is represented in Table I.

TABLE I. AVERAGE AGES

	YEARS
Entire group	24.1
Primiparas	19.7
Multiparas	29.0

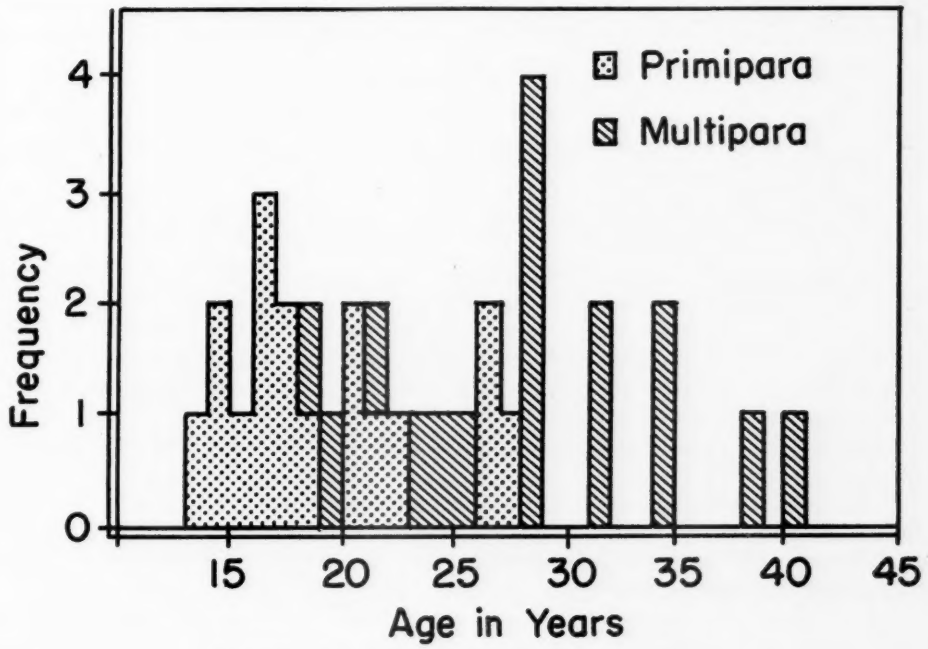

Chart 1.—Age, frequency, and parity distribution.

The parity of eclamptic patients has always been a great source of interest and speculation. Our figures fail to confirm the fact that the primiparous patient is more subject to severe eclamptic toxemia. Seventeen (51.5 per cent) of these patients were primiparas, while sixteen (48.5 per cent) had had previous pregnancies. These figures are at considerable variance from those given for eclampsia in general. DeLee[1] reports a ratio of primiparas to multiparas of 3:1, while Stander[2] quotes Hinselmann with a ratio of 6:1. Our ratio for fatal eclampsia is 1.1:1.

The significance of this considerable difference must be interpreted in the light of several factors. The first is the observation that the multiparous group is about ten years older than those pregnant for the first time. Secondly, as we will soon show, an appreciable portion of these multiparous patients had had

TABLE II. PARITY

	NUMBER OF CASES	PER CENT
Primiparas	17	51.5
Multiparas	16	48.5

previous toxemias of pregnancy. The stress of such toxemias upon the organism cannot be denied; whether any damage residual to that stress remained, however, is not certain. Finally, we may postulate that eclampsia *per se* is a much more severe condition and more likely to prove fatal in the multiparous woman. However, the latter hypothesis awaits further study.

The factor of racial distribution presents itself in this group of patients. Twenty-one of the cases occurred in Negro women; one was Indian. This is probably not evidence of racial susceptibility, but rather reflects the nature of the local population. It cannot be ignored that a gravid Negro woman probably faces greater handicaps in enduring pregnancy than a white woman of equal economic status. Moreover, negligence in seeking prenatal care and in executing proper medical instruction is a major contributing factor among these people. The racial incidence is demonstrated in Table III.

TABLE III. RACIAL INCIDENCE

	NUMBER OF CASES	PER CENT
White	11	33
Negro	21	64
Indian	1	3

The importance of prenatal care arises in this series of cases. Surprisingly enough, ten (30 per cent) of these patients had some prenatal medical attention. This was administered, for the most part, by a local physician in a rural area. In only one case (28) was there a history of frequent visits to the doctor during gestation. This patient was perfectly well until twenty-four hours before admission, when the onset of the toxemia was abrupt and most severe. The nature of this case is of greatest interest and will be discussed in some detail later.

Family history here, as in any other disease entity, may or may not be of significance. Seven (21 per cent) of these patients had a family history of hypertension. Of particular interest is the patient in Case 5, who had three sisters dying of fatal eclampsia.

Of much greater interest, however, is a review of the past histories among the 16 multiparous patients. Eleven had shown the signs and symptoms of pre-eclamptic toxemia in at least one of their previous pregnancies. Five of these 11 patients had had clinically recognized eclampsia previously.

TABLE IV. INCIDENCE OF PREVIOUS TOXEMIA

	NUMBER OF CASES	PER CENT OF ALL MULTIPARAS
Pre-eclamptic toxemia	6	38
Eclampsia	5	31
Total toxemia	11	69

The past histories of the primiparous patients were of no significance.

A review of the symptoms prior to admission is illustrated in Chart 2. It will be seen that headache, edema, and convulsions were most outstanding. Twenty of the patients had at least one generalized seizure prior to admission. Of the remaining 13, five had seizures subsequent to their arrival. The other eight, as has been mentioned previously, never had convulsions prior to death. However, these fulfill our criteria for eclampsia by demonstrating focal hyaline necroses of the liver.

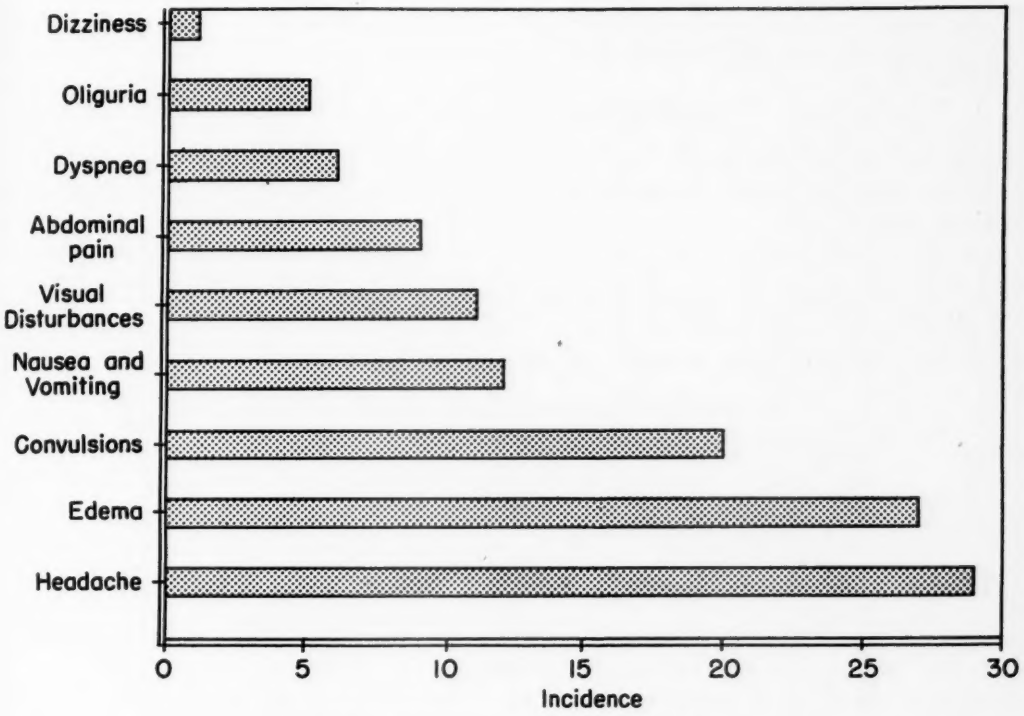

Chart 2.—Symptoms prior to admission.

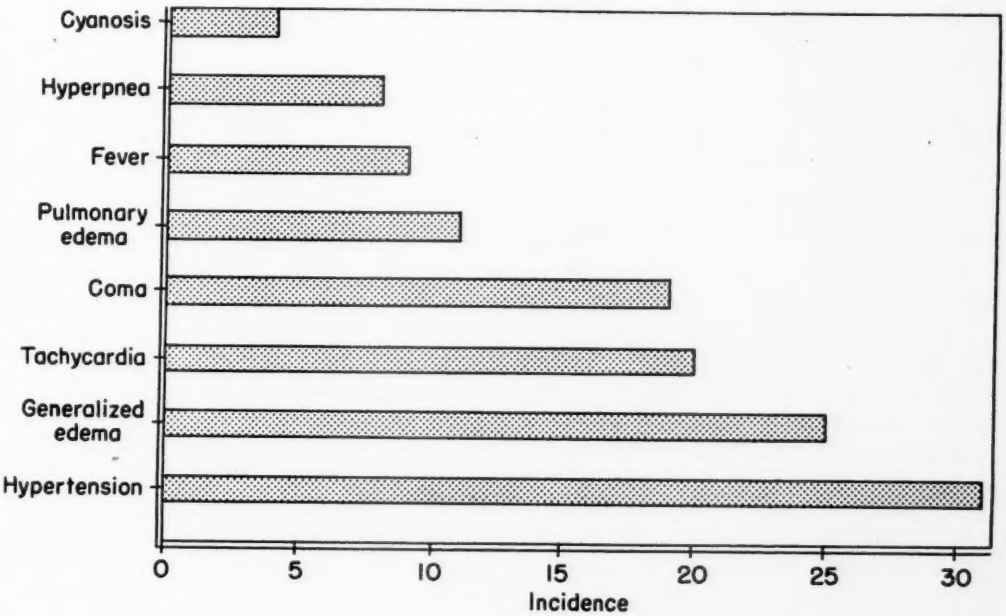

Chart 3.—Physical findings on admission.

Of secondary frequency among the symptoms were recent nausea and vomiting, visual disturbances, and abdominal pain. These were present in about one-third of the cases. Additional symptoms consisted mainly of dyspnea, oliguria, and dizziness.

The principal physical findings on admission are displayed in Chart 3. Hyperetension was present in 32 cases, the thirty-third being in shock (blood pressure 80/40) on arrival. This patient expired in the emergency room within twenty minutes. Our criterion for hypertension is a blood pressure in excess of 140/90.

Twenty-five patients (78 per cent) demonstrated generalized edema, while 19 (69 per cent) were in coma. A tachycardia of 100 or more existed in 20 patients. Pulmonary edema was present in 11 patients. Fever of 38° C. or higher was found in nine (28 per cent); hyperpnea of 30 respirations per minute or more was noted in eight. Four patients were cyanotic.

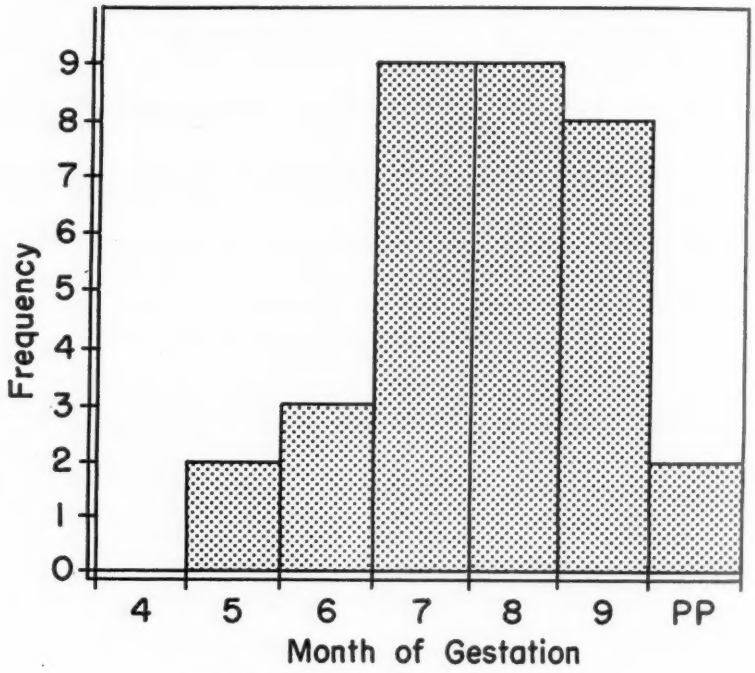

Chart 4.—Duration of pregnancy.

Since the blood pressure is an all-important sign in toxemia, an attempt has been made to classify the degree of hypertension as mild, moderate, or severe on the following basis:

1. Severe hypertension: either a systolic pressure over 200 or a diastolic pressure over 120
2. Moderate hypertension: either a systolic pressure between 160 and 200, or a diastolic between 100 and 120
3. Mild hypertension: either a systolic between 140 and 160, or a diastolic between 90 and 100.

On the basis of the above criteria, the hypertension can be classified as severe, 58 per cent; moderate, 30 per cent; and mild, 9 per cent of the cases. This is demonstrated in Table V.

The duration of the various pregnancies at the time of hospital admission are represented in Chart 4. It will be seen that two cases were post partum,

TABLE V. DEGREE OF HYPERTENSION ON ADMISSION

	NUMBER OF CASES	PER CENT
Mild	3	9
Moderate	10	30
Severe	19	58
Shock	1	3

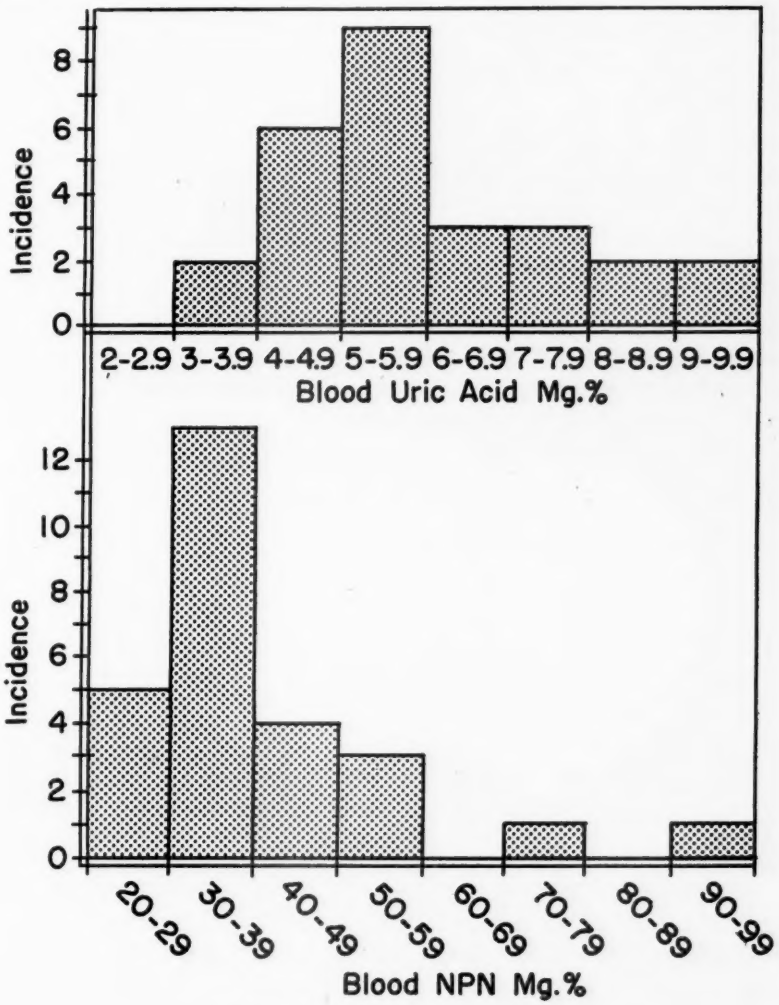

Chart 5.—Blood chemistry on admission.

and that the peak frequency was in the eighth calendar month. The average duration of pregnancy for this series was 7.6 months.

The blood chemistry findings are of considerable interest. Kaplan,[7] in his paper on blood chemistry studies in normal pregnancy and eclamptogenic toxemia, reports increases in both the non-protein-nitrogen and the uric acid levels in the blood in eclampsia. Inspection of Chart 5 will reveal that the non-protein-nitrogen is only slightly increased, the average determination being 37.2 mg. per cent. This is somewhat distorted by two high values of 91 and 70 mg. per cent in Cases 5 and 17, respectively. Therefore, in general, we can say that the increase in non-protein-nitrogen is minimal. The readings for

uric acid, however, are of considerable more significance. The mean value here is 5.88 mg. per cent.

The two graphs have been centered by placing the 4 mg. per cent value for uric acid over the 40 mg. per cent value for NPN, taking these two as the upper limits of normal. It will be seen that the peak of the graph for uric acid is considerably to the right of that for the non-protein-nitrogen.

Plasma protein determinations were performed in seven patients. The average total plasma protein was 4.97 Gm. per cent with an albumin-globulin ratio of 0.84. This is compared with those values obtained by Møller-Christensen and Thygesen,[8] who determined these values in a series of nonfatal eclampsia as a total protein of 5.61 Gm. per cent and an A/G ratio of 1:10. It will be noted that our values are considerably lower.

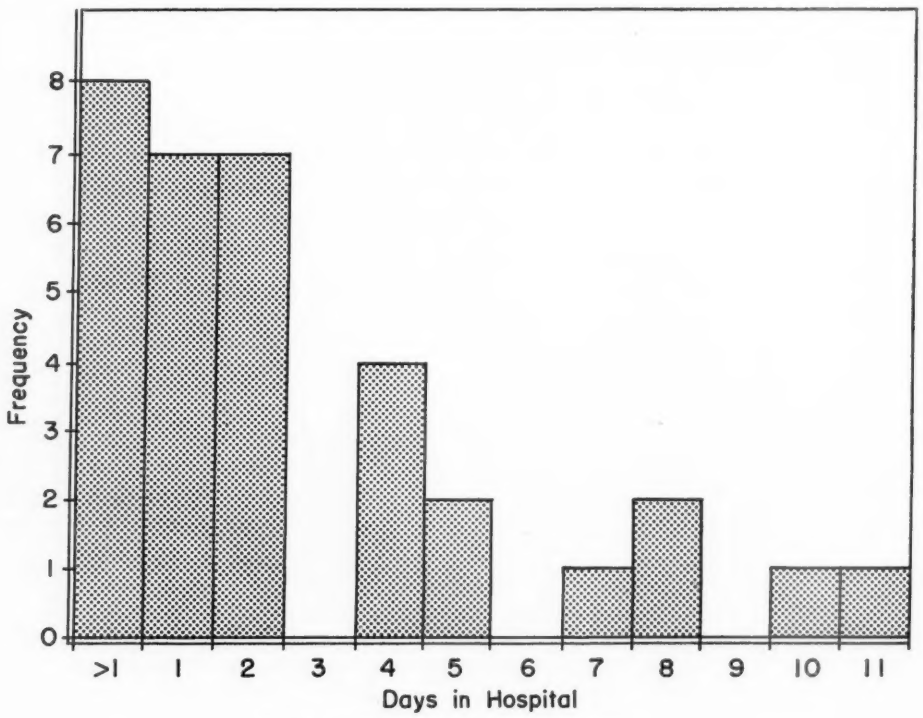

Chart 6.—Hospital stay prior to death.

The duration of stay in the hospital prior to death is of some interest. Eight patients expired within the first twenty-four hours, and seven subsequent deaths occurred on each of the two succeeding days. Therefore, within the first 72 hours, 22 (67 per cent) had expired. The arithmetic average for the group was 2.88 days, but this is considerably distorted by two cases (17 and 24), who remained alive 10 and 11 days, respectively. The distribution is given in Chart 6.

By summarizing the essential clinical aspects of these fatal cases of eclampsia, we can create a composite picture of the average patient.

If a primipara, the patient is about 19 years of age, Negro (in this area only), and has had at least one convulsion prior to admission. During the few days or weeks preceding admisssion she has experienced increasingly severe headaches and edema. She may also complain of one of the three following symptoms: recent nausea and vomiting, visual disturbances, or abdominal

pain. Physical examination reveals that she has hypertension and generalized edema and is in a comatose condition. Tachycardia and pulmonary edema may or may not be present.

If a multiparous patient, she is about 29 years of age, either white or Negro, and has had the signs and symptoms of pre-eclamptic toxemia during a previous pregnancy. There is one chance in three that she has had a previous attack of eclampsia. She, too, is comatose and demonstrates hypertension and edema. In all probability, she has had convulsions prior to admission.

Both patients will demonstrate a slight increase in blood non-protein-nitrogen and a definite increase in blood uric acid. Total plasma proteins will be reduced, and the albumin-globulin ratio markedly reduced. Death will ensue in about two days.

Anatomic Lesions

In the following section are presented the pertinent anatomic changes in the above cases. This will be followed by an attempted correlation of the various lesions in an effort to gain insight into the pathogenesis of this disease syndrome.

Liver.—The liver is the seat of an important pathologic change. The lesion most frequently encountered is a focal hyaline or fibrinoid necrosis of the liver cells, usually, but not necessarily, in the periportal areas.

The most characteristic aspect of this lesion is its variability in extent and severity. At times, it is utterly impossible to demonstrate hepatic necrosis, although its presence cannot be eliminated without study of serial sections of the entire organ. At other times the process is extremely widespread so that viable or normal appearing liver tissue is relatively scarce. Occasionally the disease process may be extremely widespread in one lobe of the liver, while the remainder appears relatively unaffected. Generally speaking, the majority of the cases show an affection between these two extremes.

In an effort to correlate the absence of hepatic necrosis with the duration of symptoms prior to death, Cases 2, 8, and 19 are examined. The patient of Case 2 presented her first symptom, headache, only a few hours before admission. She remained in the hospital for twenty-four hours before her exitus. However, the patient of Case 8 had a history of previous eclampsia and the symptoms of toxemia for at least one month; her stay in the hospital was two days. Likewise, Case 19 had had symptoms for four months before admission. Therefore, it appears that we cannot correlate the absence of hepatic lesions with a short duration of symptoms. Apparently other factors enter into the production of the necrosis.

The nature of these focal hyaline or fibrinoid lesions is of considerable interest. They are characteristically small in size and approximately fill one high-power microscopic field under 440X magnification. Adjacent hepatic cells usually involving three to five cords or more in a periportal area lose their distinct cellular outline and take on a brighter and lighter hue with the eosin. Their nuclei have disappeared, and the cell borders seem to run together without a definite line of demarcation. There may or may not be hemorrhage in the immediately surrounding area. The amount of hemorrhage has not been very impressive in these cases, althought it is frequently found beneath the liver capsule without any apparent associated hyaline necrosis. When it does occur deep in the liver substance, it is usually extensive and macroscopically visible.

Many of the lesions fail to evoke an inflammatory reaction. Often, however, these necroses result in the appearance of polymorphonuclear leucocytes at their periphery. Case 30 demonstrates widespread focal fibrinoid necrosis with an accompanying acute inflammatory reaction. Likewise, Case 28 and Case 24 show

the same cellular reaction. However, Case 24 demonstrates multiple focal fibinoid necroses limited to one lobe without cellular response. This lack of leucocytic reaction prevails in the majority of cases in which liver necrosis was present.

This observation has led us to believe that the majority of the necroses are of very recent origin.

Careful examination of the liver sections on those multiparous patients who had a history of previous toxemia fails to reveal any evidence of scarring. This suggests that whatever hepatic lesions occurred have healed without scarring and that the process is reversible.

It cannot be denied that gross impairment of function of an organ can exist without any visible anatomic alteration. However, in the presence of widespread areas of normal- appearing hepatic tissue, in many cases it is most difficult to explain the functional changes in eclampsia on the basis of the hepatic lesions.

Kidney.—Renal changes have been observed by a varitey of authors. Löhlein[9] first described the glomerular changes which he construed to be those of glomerulonephritis. Later, Fahr[10] differentiated these from glomerulonephritis and called them glomerulonephrosis. Finally, Bell,[11] in 1932, clearly defined these changes and considered them characteristic of eclampsism.

The glomeruli are usually avascular and devoid of erythrocytes, although at times they may be the seat of acute congestion. Congestion is evident when there is pronounced heart failure and accompanying congestion of all of the abdominal viscera. Congestion may also be seen occasionally when septicemia is present. There is also a definite increase in the endothelial cells in the glomerulus, as indicated by the increase in nuclei present. Also, one may see fibrinoid or hyaline necrosis of a glomerular tuft, which may spread to involve the entire glomerulus. The capillary basement membrane is conspicuously thickened and may even be duplicated.

In the preglomerular arteriole there is swelling of the wall, which may then undergo necrosis or hyalinization. If it be necrosis, there is usually thrombus formation which may extend further into the glomerulus itself.

Occasionally there is fibrosis beneath Bowman's capsule, but this is not a prominent feature.

Tubular changes have long been described as the prominent renal lesion in eclampsia, and some authors[12] still consider them the outstanding feature. Zimmerman and Peters,[13] in reviewing fatal cases of toxemia, laid considerable stress upon tubular changes. However, the incidence of pyelitis and pyelonephritis in their series was extremely high. The presence of retrograde infection and inflammation from the renal pelvis undoubtedly alters the tubular picture.

We have not been impressed by the tubular changes. It is true that there is cloudy swelling and some colloid degeneration of the tubular epithelium, but this is a highly nonspecific reaction and is seen in a wide variety of disease processes. Emphasis in the past has been placed on the presence of fat droplets within the tubular epithelium. Fat stains have been performed upon a number of these sections, and the presence of fat has been demonstrated. However, it is far less prominent than is usually seen in chronic glomerulonephritis. Indeed, in some of these sections the fat was more prominent in the glomeruli than it was in the tubular epithelium.

Erythrocytes are commonly seen in the tubules. It is our impression that this is most prominent when there is glomerular congestion.

Changes in the renal pelvis in this series are of minor importance. Only two cases (1 and 26) show evidence of pyelitis, and this is of a chronic, apparently inactive nature.

All of the changes described above are qualitative in nature and represent progressions of the same underlying pathologic process. To our knowledge no one has attempted to estimate these lesions quantitatively. Therefore, since it appeared to us that the renal changes fall into three general groups, we have established three stages which we think represent progressive degrees of kidney damage in eclampsia.

Stage 1 represents the earliest level of renal damage. It is characterized by the presence of usually avascular glomeruli with an increase in the glomerular nuclei. There is usually moderate thickening of the capillary basement membrane. In this stage there is *no* thickening of the arteriolar wall. Of these 33 fatal cases, 11 fall into this group.

TABLE VI. STAGES OF RENAL LESIONS IN ECLAMPSIA

Stage 1:	a. Avascular glomeruli (±)
	b. Increase in glomerular nuclei
	c. No visible change in arterioles
	d. Moderate thickening of basement membrane (±)
Stage 2:	a. Avascular glomeruli (±)
	b. Increase in glomerular nuclei
	c. Arteriolar thickening
	d. Marked thickening of basement membrane
	e. Fibrinoid changes in glomeruli and arterioles (±)
Stage 3:	a. Scattered obliterated hyalinized glomeruli
	b. Fibrosis beneath Bowman's capsule (±)
	c. Generalized arteriolosclerosis
	d. Kidney of arteriolonephrosclerosis

The essential difference between Stages 1 and 2 is the finding in the latter group of thickening of the arteriolar wall. It has been suggested that this early change may be attributable to edema. There may or may not be fibrinoid changes in the glomeruli. If the fibrinoid changes are evident in the glomeruli, there is usually an involvement of the arteriole, as well. Sixteen of our cases are in this group.

Stage 3 represents the development of lesions remarkably similar to those of nephrosclerosis. There is a diffuse arteriolo- and arteriosclerosis. There are scattered obliterated, hyalinized glomeruli. Occasionally one sees fibrosis beneath Bowman's capsule. Six of these cases are in Stage 3.

In Table VI are listed the criteria for the foregoing classification.

The results of the analysis of the cases in each stage are shown in Table VII. It will be seen that the percentage of primiparous patients drops from 82 per cent in Stage 1 to 50 per cent in Stage 2, and to 0 in Stage 3, while the proportion of multiparas rises from 18 per cent to 50 per cent, then to 100 per cent. Likewise, with one exception (Case 8), the multiparous patients with a history of preceding toxemia are confined to Stages 2 and 3. The average age for each group rises from 19.3 years to 25.2, to 30.8 in the progressive stages of renal injury. The average duration of symptoms in all stages is practically the same: 26.6, 25.3, and 28.4 days.

Although there are reports to the contrary,[15, 16] it is generally agreed that the permanent vascular and renal lesion residual of eclampsia and pre-eclamptic toxemia is not glomerulonephritis, but arteriolonephrosclerosis. Dexter and Weiss[3] remark that the post-toxemic hypertension does not differ from the syndrome of benign or malignant nephrosclerosis. Likewise, the histologic picture is that of benign or malignant nephrosclerosis. Similar observations have been reported by Herrick and Tillman.[14]

It has been shown by Reid and Teel[17, 18] that hypertension residual to toxemia is largely dependent upon the duration of the toxemia. It also appears that the degree of hypertension during the toxemia is another factor of im-

TABLE VII. ANALYSIS OF STAGES OF RENAL DAMAGE

	STAGE		
	1	2	3
Total Cases:	11	16	6
Primiparas	9	8	0
Multiparas	2	8	6
No previous toxemia	1	2	2(?)
Previous toxemia	1	6	4
Pre-eclampsia	0	4	2
Eclampsia	1	2	2
Average in years	19.3	25.2	30.8
Duration of symptoms in days	26.6	25.3	28.4

portance.[19] This suggests certainly that the hypertension occurs before any anatomic alteration of the vascular system is visible, and that these arteriolar changes are secondary to the hypertension. This is substantiated by the observation of the lesions in Stage 1.

Finally, it must be remembered that all of these cases are fatal, and the fact that the renal lesions have progressed only to Stage 1 does not preclude a fatal outcome.

Adrenals.—The lesions found in the adrenal glands have been a source of great interest and investigation. Essentially they consist of necrosis and hemorrhage of varying degrees. The knowledge that this damage occurs in eclampsia is not new; indeed, it is described by Dexter and Weiss[3] in conjunction with a case report of fatal cortical necrosis of the kidneys occurring in eclampsia. Other authors have reported it as an incidental finding in cases of fatal toxemia.[13] However, considerably more attention should be devoted to this lesion.

Eleven (33 per cent) of these patients showed this pathologic change in the adrenal glands. Of these, 45 per cent were classified as severe in that practically no functional adrenal cortical tissue remained. The other 55 per cent showed involvement of approximately half of the cortical tissue. There were no cases with minimal lesions. The distribution of the cases is shown in Table VIII.

TABLE VIII. DEGREE OF ADRENAL DAMAGE

CASE NUMBER	DEGREE
1	Moderate
4	Severe
13	Moderate
18	Severe
20	Moderate
21	Moderate
23	Moderate
24	Severe
27	Moderate
29	Severe
32	Severe

However, examination of the clinical histories of these patients lends new significance to the appearance of this lesion. Initially, attention should be directed to a point strongly emphasized by Dexter and Weiss, namely, that normal blood pressure in toxemic patients does not preclude the presence of shock. They maintain that, after a marked hypertension, a reduction to normal levels, and not below, may be coincident with the existence of the shock syndrome.

A review of the cases in this series presenting severe damage to the adrenals reveals that all are primiparas except Case 32. We can offer no explanation for this. Case 4 expired undelivered twenty-four hours after ad-

TABLE IX. SUMMARY OF THE CLINICAL HISTORIES

CASE	AGE	RACE	PARITY	FAMILY HISTORY OF HYPER-TENSION	PREVIOUS TOXEMIA		SYMPTOMS PRIOR TO ADMISSION							
					PRE-ECLAMP-TIC	ECLAMP-TIC	SEVERE NAUSEA AND VOMIT-ING	EDEMA	HEAD-ACHE	DYSPNEA	ABDOM-INAL PAIN	CONVUL-SIONS	OLIG-URIA	VISCERAL DISTURB-ANCES
1	29	C	2-0-2	+	+		+	+	+	+				
2	18	C	P						+			+		
3	18	W	P				+	+	+	+		+	+	+
4	17	C	P				+	+	+	+		+		
5	19	C	1-0-1	+				+	+		+	+		
6	27	C	P					+	+		+	+	+	
7	39	C	10-2-8			+		+				+		+
8	29	W	3-2-0			+		+	+		+	+		
9	17	C	P					+	+		+			
10	41	W	8-0-5		+			+	+				+	+
11	14	C	P				+	+	+		+	+		
12	26	C	5-1-2		+			+	+			+		+
13	16	C	P					+	+			+		
14	15	C	P	+				+	+					+
15	32	C	8-1-7			+								
16	28	C	P				+	+	+	+				
17	35	I	9-0-9				+	+	+	+	+		+	
18	23	C	P					+	+		+		+	
19	17	C	P				+		+		+	+		
20	24	W	2-0-2		+		+	+	+			+		
21	29	C	1-0-0	+			+	+	+			+		+
22	22	C	3-0-3				+	+	+			+		
23	27	W	P						+			+		
24	15	C	P					+	+			+		
25	21	C	P					+	+			+		+
26	35	W	3-0-3			+	+	+	+					+
27	20	C	2-0-2	+	+			+	+					
28	22	W	P	+					+			+		+
29	21	W	P					+	+			+		+
30	19	W	P									+		
31	29	W	2-0-0	+		+		+						
32	32	W	6-0-6		+			+	+	+				
33	25	C	2-2-0				+	+	+		+			
Total					**6**	**5**	**12**	**27**	**29**	**6**	**9**	**20**	**5**	**11**

TABLE X. SUMMARY OF HOSPITAL DATA

CASE	(ON ADMISSION) BLOOD PRESSURE	PULSE	RESP.	TEMP. ° C.	COMA	GENERALIZED EDEMA	PULMONARY EDEMA	CYANOSIS	DURATION OF PREGNANCY (MO.)	CHEMISTRY NPN	CHEMISTRY UA	PROTEINS TOTAL	PROTEINS A/G	CO_2 COMBINING POWER	W.B.C.	HOSPITAL STAY	TERMINAL SHOCK
1	240/140	100	30	38		+		+	7	54	7.6			34	8,200	2 d.	+
2	164/124	160		40	+	+	+		8	38	9.6				16,100	2 d.	
3	180/116	140		37.2	+	+	+	+	7½							3 hr.	
4	200/132	96	36	38.7	+	+	+		7						11,100	1 d.	
5	170/120	126	30	39.8	+	+	+		9	91	8.4			28.2		? hr.	
6	172/86	132	34	38.2	+	+	+		7	38	6.0			46.6		9 hr.	
7	230/184	134	28	37		+	+		8	36	5.6			12.6		2 d.	+
8	180/130	132	32	38.2	+	+	+	+	9	38	5.3			26.8	21,950	2 d.	
9	176/134	128		37	+	+		+	8½	20	5.2			40	8,200	2 d.	
10	240/130	138	20	36.8					7	36	3.3			50		1 d.	
11	170/140	108	40	37.4	+	+	+		9	27	6.1	4.1	1.2	48		7 d.	
12	170/140	134	26	36.5	+				7	44	8.4			51	20,200	2 d.	
13	190/110	100	20	37.6	+	+	+		9	56	5.9	4.0	0.93	30	14,400	1 d.	+
14	180/140	88	22	37					7½	30	7.3			35	6,020	4 d.	
15	210/160	100	22	37.2		+			7	38	4.8				22,500	1 d.	
16	190/110	136	30	36.8		+	+		9	35	4.6			39	15,000	4 hr.	
17	250/170	110	24	37.7		+			7	70	6.1	4.4		40	22,920	11 d.	+
18	200/110	104	26	38.2		+			5½	31	3.7				22,400	8 d.	
19	80/40		30		+				9							20 min.	
20	146/100	74		36.7	+	+			9	53	5.2					4 d.	+
21	190/95	110	22	38	+	+			7	42	5.6			47	6,950	2 d.	+
22	216/198	90		38.1	+	+	+		6	48	4.7					1 d.	
23	138/98	80		37.1					6	33	4.0					8 d.	+
24	175/120	88	18	36.8	+	+			9	20	4.5			49	9,600	10 d.	+
25	220/150	90	16	37.7	+	+			6							3 hr.	
26	220/130	88	20	36.5					8½	30	7.3	5.1	1.1	47		1 d.	
27	300/180	94	24	37		+			7	25	5.0	5.0	0.72	56	8,200	5 d.	+
28	155/105	100	26	37.4	+	+			7						17,000	12 hr.	
29	166/120	100	14	37		+			9	35	5.0	3.9	0.89	26	23,840	5 d.	+
30	156/100	90	20	37.4	+				8	41	9.2	8.3	0.79	47	11,400	2 d.	
31	252/108	120		36	+	+			8½						22,000	? hr.	
32	275/170					+			8	35	4.9				10,200	4 d.	+
33	180/130	72	20	37					9	23	5.7				8,500	4 d.	
Total					19	25	11	4									11

TABLE XI. SUMMARY OF PATHOLOGIC FINDINGS

CASE	HEART				BRAIN			FOCAL NECROSIS OF LIVER	FOCAL NECROSIS PANCREAS	STAGE OF RENAL LESION	ADRENAL NECROSIS AND HEMORRHAGE	PNEUMONIA	PULMONARY EDEMA	HYDROTHORAX	ENDOMETRITIS	CYSTITIS
	NECROSIS	HEMORRHAGE	MYOCARDITIS	ENDOCARDITIS	NECROSIS	HEMORRHAGE	ARTERITIS									
1	+	+						+		2	+					
2										2		+	+			
3								+		1			+			
4		+						+		1	+	+	+			
5	+	+						+		1		+	+		+	
6								+		2		+	+			
7		+						+		2		+				
8		+								1			+		+	
9		+		+				+		1		+			+	
10								+		2					+	
11					+		+	+	+	1					+	
12								+	+	3		+				+
13		+						+		1	+		+	+		
14		+						+		2		+	+		+	
15								+		3					+	
16								+		2		+	+	+		
17	+		+					+		3		+				
18								+		1	+	+	+			+
19										1			+	+		
20								+		2	+		+		+	
21								+		2	+					
22								+		2		+				
23			+					+		2	+		+		+	+
24								+		2	+					+
25	+					+	+	+		2		+				
26							+			3			+			+
27		+						+		2	+			+		
28								+	+	1				+		
29								+		1	+					
30		+				+		+	+	2		+	+			
31		+				+	+	+		2		+	+			
32		+						+		3	+	+				
33								+		3					+	
Total	4	12	2	1	1	3	4	29	4		11	16	16	5	10	5

mission, apparently of pulmonary edema that failed to respond to therapy. Case 18 expired in coma eight days after admission and six days after the delivery of a macerated fetus. At the time of death she had a rising NPN and gross hematuria. Case 24 delivered a living child four days after admission and expired six days later. The signs of toxemia were rapidly diminishing in this patient; albuminuria, hematuria, and casts were decreasing. Case 29 delivered on the fifth hospital day; the blood pressure dropped from 300/116 to 90/70 during a three-hour period, and the patient apparently died in shock. Case 32 had a rise in pulse rate and temperature on the fourth hospital day, together with a sudden drop in blood pressure from 270/170 to 120/0, followed shortly by death.

A review of the patients with adrenal lesions of moderate degree reveals that four of the six are multiparas. Case 1 is a patient who died in shock several hours post partum. However, there was focal necrosis of the myocardium with a complete heart-block, as revealed by the electrocardiogram. Since the patient complained of angina, the hypotension was probably cardiac in origin. Case 13 delivered a stillborn fetus on the second hospital day and stopped breathing soon after delivery, the blood pressure being unobtainable. Case 20 delivered a live baby on the second hospital day, remained in deepening coma, and expired two days later. In these adrenals the necrosis is early but extremely widespread. Case 21 delivered a stillborn fetus on the second hospital day and expired in coma and questionable shock fifteen hours later. Case 23 delivered a macerated fetus on the seventh hospital day, developed shock (BP 100/60) unrelieved by blood and plasma, and expired twenty-four hours later. Case 27 delivered on the fifth hospital day, the blood pressure dropped from 300/180 to 90/70 over a period of hours, and the patient expired in shock.

The remaining cases, in whom no adrenal damage is evident, are examined for the shock-like picture. Only two need be considered. Case 7 developed shock postpartum, responded to intravenous fluids, and then developed pulmonary edema, which failed to respond to the usual therapy. Case 17 had hysterotomy and developed shock four days later, which was successfully treated with fluids. This patient probably died of pneumonia and myocarditis.

In summarizing the adrenal changes, it appears that there is a possible relationship between the adrenal damage and the terminal appearance of the shocklike syndrome. In the light of the many widespread lesions in other viscera, it would be gross misinterpretation to say that the sole cause of death was adrenal insufficiency. However, it does appear that adrenal insufficiency secondary to recent widespread injury may be a contributing factor in the exitus of certain patients. A similar mechanism is already known to exist in meningococcemia, resulting in the Waterhouse-Friderichsen syndrome.[25-27] We do know that hypertensive and toxemic patients tend to show a marked drop in blood pressure after delivery.[20-24] If sufficient adrenal damage were to exist in such a patient, she might tolerate that hypotension very poorly and fail to respond.

Additional Lesions.—Pathologic changes in the other viscera will be discussed under a combined heading and are demonstrated in Chart 7.

The lungs showed pneumonia of varying degrees in 16 of the cases. These infections were usually marked by pulmonary edema which failed to respond to the usual therapy. An associated purulent bronchitis was present in four of these cases.

Of considerable clinical interest was the presence of unrecognized bilateral hydrothorax: Case 13, 550 c.c. and 450 c.c.; Case 16, 1,000 c.c. and 1,000 c.c.; Case 19, 500 c.c. and 500 c.c.; Case 27, 300 c.c. and 200 c.c.; Case 28, 700 c.c. and 450 c.c. Whether the removal of such fluid would have altered the outcome is highly debatable.

Acute endometritis was present in ten cases. This is probably of significance only in those cases which developed septicemia.

The heart was the site of hemorrhage in twelve patients. Four of these showed focal necrosis of the myocardium with slight cellular reaction. There were two cases of myocarditis, one characterized by the focal aggregation of polymorphonuclear leucocytes, and the other by a diffuse scattering of round cells. There was one case of focal acute endocarditis. Idiopathic focal necrosis of the myocardium has been described[28] as occurring in normally pregnant women, but we can see no similarity between the reported lesion and those of our own cases.

The pancreas demonstrated focal necrosis in four cases. We consider this to be of no particular significance, save that it is a manifestation of the underlying mechanism of damage in the pathogenesis of eclampsia.

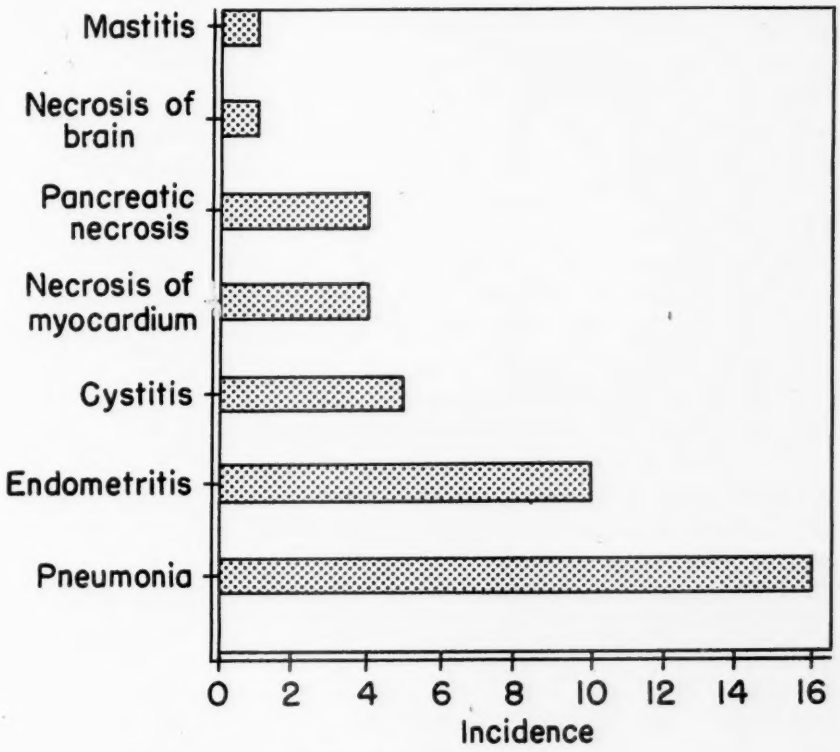

Chart 7.—Additional lesions.

Cystitis was present in five cases.

Acute purulent mastitis was found in one case.

Focal necrosis of the brain was present in one case. Cerebral hemorrhage was also present in three cases. In two (Cases 25 and 31) this hemorrhage was massive. These two cases, as well as Cases 21 and 26, demonstrated cerebral arteritis and arteriolitis with necrosis of the vessel walls.

Discussion

The interpretation of these lesions is a fascinating and highly complex problem. Each visceral change becomes important, not only because it reflects the mechanism of its own production, but because it, too, in turn, may be of

mission, apparently of pulmonary edema that failed to respond to therapy. Case 18 expired in coma eight days after admission and six days after the delivery of a macerated fetus. At the time of death she had a rising NPN and gross hematuria. Case 24 delivered a living child four days after admission and expired six days later. The signs of toxemia were rapidly diminishing in this patient; albuminuria, hematuria, and casts were decreasing. Case 29 delivered on the fifth hospital day; the blood pressure dropped from 300/116 to 90/70 during a three-hour period, and the patient apparently died in shock. Case 32 had a rise in pulse rate and temperature on the fourth hospital day, together with a sudden drop in blood pressure from 270/170 to 120/0, followed shortly by death.

A review of the patients with adrenal lesions of moderate degree reveals that four of the six are multiparas. Case 1 is a patient who died in shock several hours post partum. However, there was focal necrosis of the myocardium with a complete heart-block, as revealed by the electrocardiogram. Since the patient complained of angina, the hypotension was probably cardiac in origin. Case 13 delivered a stillborn fetus on the second hospital day and stopped breathing soon after delivery, the blood pressure being unobtainable. Case 20 delivered a live baby on the second hospital day, remained in deepening coma, and expired two days later. In these adrenals the necrosis is early but extremely widespread. Case 21 delivered a stillborn fetus on the second hospital day and expired in coma and questionable shock fifteen hours later. Case 23 delivered a macerated fetus on the seventh hospital day, developed shock (BP 100/60) unrelieved by blood and plasma, and expired twenty-four hours later. Case 27 delivered on the fifth hospital day, the blood pressure dropped from 300/180 to 90/70 over a period of hours, and the patient expired in shock.

The remaining cases, in whom no adrenal damage is evident, are examined for the shock-like picture. Only two need be considered. Case 7 developed shock postpartum, responded to intravenous fluids, and then developed pulmonary edema, which failed to respond to the usual therapy. Case 17 had hysterotomy and developed shock four days later, which was successfully treated with fluids. This patient probably died of pneumonia and myocarditis.

In summarizing the adrenal changes, it appears that there is a possible relationship between the adrenal damage and the terminal appearance of the shocklike syndrome. In the light of the many widespread lesions in other viscera, it would be gross misinterpretation to say that the sole cause of death was adrenal insufficiency. However, it does appear that adrenal insufficiency secondary to recent widespread injury may be a contributing factor in the exitus of certain patients. A similar mechanism is already known to exist in meningococcemia, resulting in the Waterhouse-Friderichsen syndrome.[25-27] We do know that hypertensive and toxemic patients tend to show a marked drop in blood pressure after delivery.[20-24] If sufficient adrenal damage were to exist in such a patient, she might tolerate that hypotension very poorly and fail to respond.

Additional Lesions.—Pathologic changes in the other viscera will be discussed under a combined heading and are demonstrated in Chart 7.

The lungs showed pneumonia of varying degrees in 16 of the cases. These infections were usually marked by pulmonary edema which failed to respond to the usual therapy. An associated purulent bronchitis was present in four of these cases.

Of considerable clinical interest was the presence of unrecognized bilateral hydrothorax: Case 13, 550 c.c. and 450 c.c.; Case 16, 1,000 c.c. and 1,000 c.c.; Case 19, 500 c.c. and 500 c.c.; Case 27, 300 c.c. and 200 c.c.; Case 28, 700 c.c. and 450 c.c. Whether the removal of such fluid would have altered the outcome is highly debatable.

Acute endometritis was present in ten cases. This is probably of significance only in those cases which developed septicemia.

The heart was the site of hemorrhage in twelve patients. Four of these showed focal necrosis of the myocardium with slight cellular reaction. There were two cases of myocarditis, one characterized by the focal aggregation of polymorphonuclear leucocytes, and the other by a diffuse scattering of round cells. There was one case of focal acute endocarditis. Idiopathic focal necrosis of the myocardium has been described[28] as occurring in normally pregnant women, but we can see no similarity between the reported lesion and those of our own cases.

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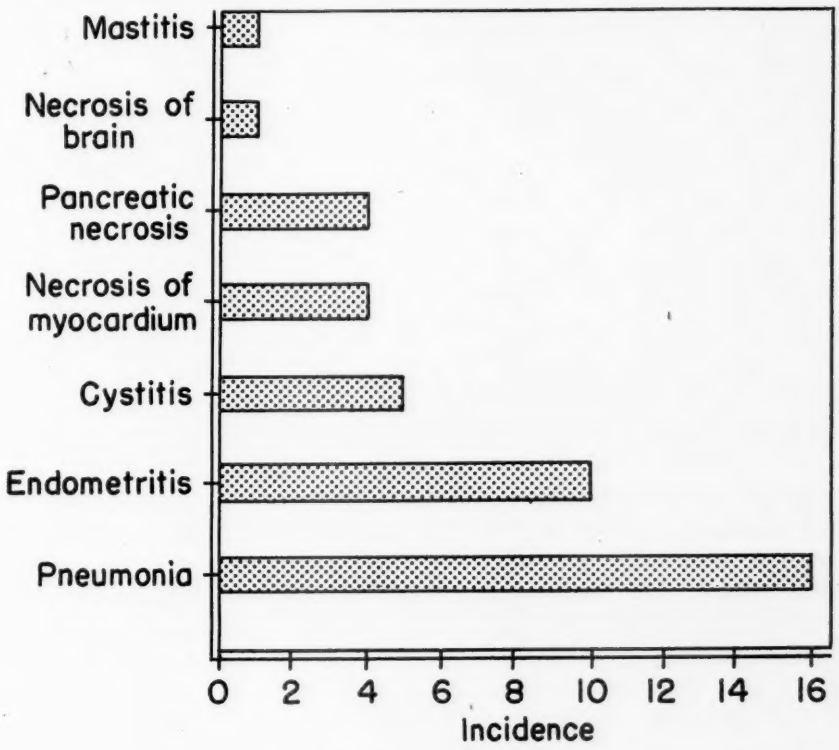

Chart 7.—Additional lesions.

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Discussion

The interpretation of these lesions is a fascinating and highly complex problem. Each visceral change becomes important, not only because it reflects the mechanism of its own production, but because it, too, in turn, may be of

such significance that it may cause the death of the patient. This is excellently demonstrated by the massive cerebral hemorrhage from necrosis of the cerebral arteries, the myocardial necrosis which led to heart failure, and the massive destruction of the adrenals which, if it did not lead to vascular collapse, probably prevented recovery from that collapse.

However, these lesions are significant aside from their immediate effects. They reflect tissue changes resulting from altered physiology of the vascular system. In the light of recent reports, the nature of the altered vascular function is considerably clarified.

The underlying mechanism of visceral damage depends upon a generalized vasoconstriction.[3, 29] This is manifested by the retinal arterioles in the toxemic patient.[30, 31] Indeed, the progress of the toxemia can be measured by daily examination of these arterioles to determine whether the vascular spasm persists, becames more accentuated, or is lessening.[32] It has also been observed in the retina that, if the vascular spasm persists, in a certain percentage of cases profound and permanent changes take place in the arterioles.[30]

Hertig[33] believes that the essential lesion exists in the precapillary arteriole and that the nature of this change is an arteriolitis. We agree that such changes can and do take place. However, it must be remembered that Goldblatt[34] in 1938 demonstrated that arterial and arteriolar changes of a comparable nature could be produced merely by the presence of hypertension. Similar results have been reported by Wilson and Byrom,[35, 36] who also found focal necrosis in the heart, pancreas, and liver as associated changes. Petechial hemorrhages were characteristic of these vascular lesions.

Therefore, it seems reasonable to postulate, as Dexter and Weiss have suggested, the following sequence of events: a vasoconstriction occurs with a resulting hypertension, which leads to small arterial and arteriolar changes; these vascular changes, together with local tissue hypoxia, result in the petechial hemorrhages and the focal necroses. The lack of change in the precapillary arterioles in our Stage 1 of the renal lesion is in accord with this hypothesis.

It may be profitable to examine these lesions in the light of certain recent observations relating to the possible mechanisms involved in the etiology of eclampsia to see if there is any correlation between the various hypotheses suggested and the anatomical changes observed. For example, Smith and Smith in a number of reports have created a most interesting hypothesis. They have isolated a euglobulin toxic factor from the menstrual flow[37, 38] and consider it to be the agent responsible for the arteriolar and endometrial changes in menstruation. A similar substance[40] has been isolated from pleural exudate by Menkin.[39] To this he has given the name "necrosin." Smith and Smith postulate that the senile changes which take place in the placenta[42] (perhaps on the basis of inadequate blood supply) result in the production of "necrosin." This in turn acts upon the vascular system of the mother. They also suggest that "necrosin" may come from any source of tissue destruction.

This seems compatible with the concept that foci of infection may play some role in the etiology of eclampsia;[43, 44] such foci would provide an extrauterine source of "necrosin." Evidence in favor of this is demonstrated in Case 28, in

which the patient had careful and frequent prenatal care. In this case the development of an acute purulent mastitis resulted in the explosive onset of eclampsia with death thirty-six hours after the first symptom. The role of infection in producing liver necrosis has been well demonstrated by Seely.[45] Likewise, Smith and Zeek,[46] in producing periarteritis nodosa by rapidly rising

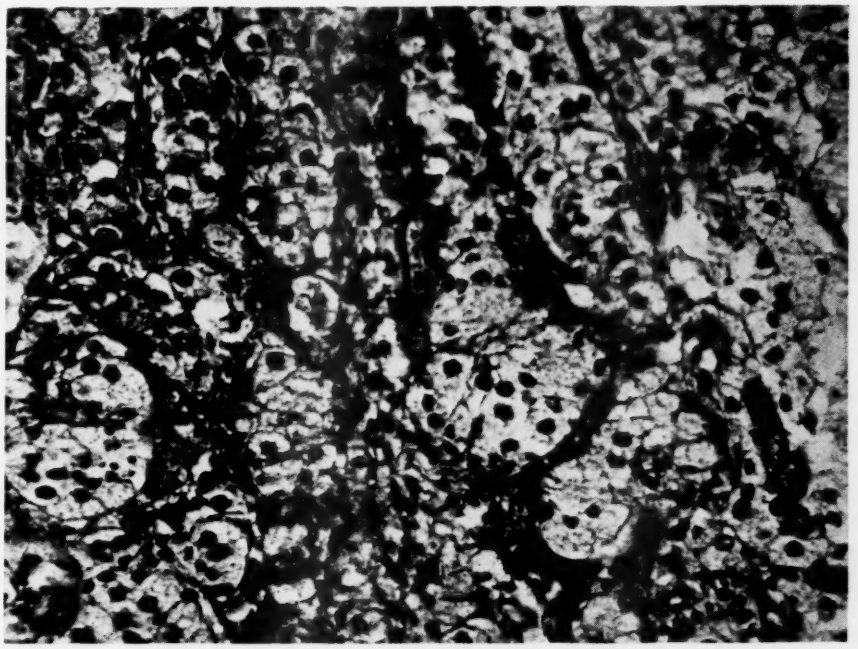

Fig. 1.—Capillary necrosis in the adrenal gland: Case 20—The photograph shows the mechanism of adrenal damage in eclampsia. The capillaries between the fascicles have undergone fibrinoid necrosis. Other areas in this gland demonstrated progression of this lesion, namely, parenchymal necrosis and hemorrhage. (×440)

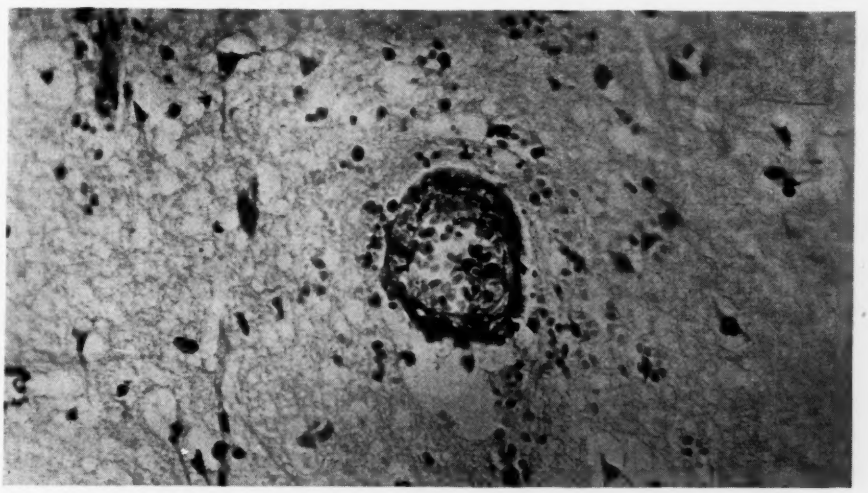

Fig. 2.—Cerebral vascular changes in eclampsia: Case 25—The photograph shows edema and necrosis of the vessel wall. Polymorphonuclear leukocytes are evident both in the perivascular space and in the wall itself. Scattered erythrocytes are present in the surrounding brain tissue. (×440)

hypertension, found a great increase in positive results when a focus of mixed infection was present.

Another very interesting observation is the fact that the vascular system in toxemic patients is far more sensitive to vasopressor substances than that of normal nonpregnant women, of normally pregnant women, and of puerperal women.[47-49] Moreover, it has been shown[49] that this is an acquired characteristic and appears some time after the seventeenth week of gestation and prior to the onset of symptoms. Other observations by Browne[49] suggest that this vascular sensitization may be caused by excessive amounts of gonadotropin. This also conforms to our concept of hormone imbalance in eclampsia, namely, decreased estrogen and progesterone and a marked increase in gonadotropin.[50-56]

The role of a pre-existing hypertension in increasing the incidence of toxemia and eclampsia is established, but not at all clear. Certain experimental work by Dill and Erickson[57] in creating hypertension in pregnant animals resulted in the appearance of lesions similar to those in eclampsia. If it could be demonstrated that hypertension, regardless of its cause, could result in uterine vascular changes which would produce relatively inadequate placental blood supply and, in turn, premature senile placental changes, then the role of pre-existing hypertension would be greatly clarified.

Further discussion of the pathogenesis of eclampsia does not fall within the scope of this study. Suffice it to say that all the lesions described reflect the profoundly altered physiology of the vascular system and, in addition, bear considerable significance in themselves with respect to the life of the patient.

Summary

1. Thirty-three fatal cases of eclampsia examined at autopsy are reviewed.

2. Analysis of the clinical histories has been presented in relation to age, parity, race, prenatal care, family history, previous medical and obstetric history, symptoms, physical findings on admission, duration of pregnancy, blood chemistry, and duration of hospital stay prior to death.

3. Hepatic lesions consist of focal fibrinoid necrosis, usually of recent origin, with or without hemorrhage.

4. Renal lesions have been divided into three stages which represent steps in the development of permanent renal change: Stage 1, with glomerular but no arteriolar alterations, was typical in 33 per cent of the cases; Stage 2, characterized by thickening of the arteriolar wall, was observed in 48 per cent of the cases; Stage 3, with lesions similar to arteriolonephrosclerosis, characterized 18 per cent of the cases.

5. Eleven cases demonstrated hemorrhage and necrosis in the adrenals, five of which were classified as severe. An attempt has been made to correlate these lesions with vascular collapse prior to death.

6. Additional lesions found were: pneumonia; focal necrosis of the myocardium, pancreas, and brain; acute endometritis; cerebral hemorrhage; cystitis; acute mastitis; and cerebral arteritis and arteriolitis.

7. An attempt is made to correlate the observed lesions with some current hypotheses concerning the pathogenesis of eclampsia.

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ELEVATED BLOOD PRESSURE IN PREGNANCY*

A Report of 1,800 Cases

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DURING the full term of gestation, the physiologic processes of the human female are placed under a severe strain of added work. Fortunately, the structures of the body are endowed with sufficient margins of safety to allow the normal woman to bear her children without resultant permanent damage to her mental and physiologic well-being. However, for the woman suffering from disease processes, either functional or organic, or for the woman whose body functions can operate safely only at normal capacity, pregnancy becomes a burden that temporarily or permanently impairs the health of the prospective mother. Of the medical problems that complicate normal pregnancy, those associated with elevated blood pressure are probably the most serious because of their relative frequency and severity.

In an attempt to better evaluate cases associated with elevated blood pressure over 140/90, the records of the Lewis Memorial Maternity Hospital were reviewed. For simplicity of study they were divided into four groups: (1) The pre-eclamptic, which included those cases that had normal pressure in their early pregnancy, but as term approached the pressure gradually or suddenly rose over 140/90. We are fully cognizant that this group will not only include the true pre-eclamptics, but also potential hypertensives, that manifest themselves as a result of the added burden of pregnancy, and those cases that are classed by some as low reserve kidney. If we err in including these cases as pre-eclamptics, the error is in the patient's favor since she comes under much closer observation. (2) This is the eclamptic group which requires no further elaboration. (3) This is the group which will be referred to as the nephritis group, exclusive of cases of ascending or pyelonephritis. (4) The fourth and last group is the hypertensive which includes all types, the etiology and classification of which is better discussed in texts of internal medicine.

Material

From 1931 to 1945, inclusive, 28,263 mothers were delivered at the Lewis Memorial Maternity Hospital. Of these, 1,800 patients, or 6.36 per cent, had a blood pressure of, or over, 140/90 during all or part of their pregnancy. Table I represents the yearly incidence of this complication. The first and last line of the table is the total for the fifteen-year period which was reviewed. Pre-eclampsia represented 1,454 cases, or 5.14 per cent; eclampsia, 51 cases, or 0.18 per cent; nephritis, 12 cases, or 0.04 per cent; and hypertension, 283 cases,

*Read at a meeting of the Chicago Gynecological Society, Jan. 17, 1947.

or 1.0 per cent. The last column on the right side of the table is the percentage of pre-eclamptics that progressed into eclampsia. This incidence was 3.4 per cent. However, it is possible also for either the nephritic or the hypertensive to develop eclampsia.

TABLE I. INCIDENCE BY YEARS OF ELEVATED BLOOD PRESSURE 140/90

		PRE-ECLAMPSIA		ECLAMPSIA		NEPHRITIS		HYPERTENSIVE		TOTAL	E P & E
	TOTAL CASES	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	PER CENT	PER CENT
1931-45	28263	1454	5.14	51	0.18	12	0.04	283	1.00	6.36	3.4
1931	1620	21	1.29	2	0.12	0	–	1	0.07	1.48	8.7
1932	2321	137	5.90	3	0.13	2	0.09	13	0.56	6.68	2.1
1933	2145	157	7.33	3	0.14	1	0.04	36	1.67	9.18	1.3
1934	2236	228	10.20	4	0.17	1	0.05	31	1.38	11.80	1.3
1935	2103	101	4.80	7	0.33	1	0.04	27	1.28	6.46	6.5
1936	2139	77	3.64	6	0.28	1	0.06	24	1.12	5.10	7.2
1937	2097	45	2.14	6	0.28	–	–	8	0.38	2.80	11.8
1938	2087	144	6.89	5	0.30	–	–	39	1.87	9.06	3.3
1939	1911	116	6.07	1	0.06	2	0.10	40	2.09	8.32	0.9
1940	1849	82	4.43	4	0.22	3	0.16	10	0.54	5.35	4.6
1941	1806	113	6.27	4	0.22	–	–	15	0.81	7.30	3.4
1942	1902	79	4.15	3	0.16	1	0.05	19	1.00	5.36	2.7
1943	1850	81	4.37	2	1.11	–	–	7	0.38	4.86	2.4
1944	1218	42	3.44	1	0.09	–	–	10	0.81	4.34	2.3
1945	979	31	3.16	–	–	–	–	3	0.31	3.47	0.0
Total	28263	1454	5.14	51	0.18	12	0.04	283	1.00	6.36	3.4

Parity.—Table II represents the parity of the 1,800 cases expressed in percentages. The pre-eclamptic group was made up of 52 per cent primiparas and 48 per cent multiparas; the eclamptic group was 80 /per cent primiparas and 20 per cent multiparas; the nephritis group was 50 per cent and 50 per cent; and the hypertensive group was 25 per cent primiparas and 75 per cent multiparas.

TABLE II. PARITY

	0	1	2	3	4	5	6	7	8	9	10
Pre-eclampsia 1,454 cases	52.3	18.5	12.6	6.8	4.2	1.9	1.6	1.2	0.5	0.2	0.2
Eclampsia 51 cases	80.3	5.8	3.9	5.8	1.9						
Nephritis 12 cases	50.0	33.3	8.3	8.3							
Hypertension 283 cases	25.4	18.6	12.5	11.1	10.3	5.4	6.8	3.2	1.8	2.1	2.9

Figures represent percentages of total. 1,800 cases, 1931 to 1945 inclusive.

Time of Elevation of Blood Pressure.—Fig. 1 is a graphic representation of the period of gestation in weeks, when the pressure became elevated in the pre-eclamptic and eclamptic groups. The former is represented by the line with open circles, and the latter by the continuous line. Suffice it to say that 90 per cent of each group first demonstrated the elevation of pressure after the thirtieth week of gestation, and the incidence rapidly rose as term approached. The week of gestation was determined by the date of the last menstrual period, and is accurate for the greatest majority. The margin of error would be a plus or minus two to four weeks.

Physical Characteristics.—The average "height" of each group was almost identical, and varied from 62.5 inches to 63.6 inches. The average "age" in

years varied from 27 to 28 years in all groups except the hypertensive, which averaged 32.3 years. The average normal "weight" varied from 127 pounds to 137 pounds, except for the hypertensive who averaged 152 pounds. The fourth line in Table III shows the "gain in weight" up to the period of gestation at which the pressure became elevated, and is 26 pounds and 27.4 pounds for the pre-eclamptic and eclamptic groups, respectively. This represents the minimum weight gained by these patients, since many of them disregarded or refused treatment, and thus gained an additional 10 to 20 pounds during the remaining weeks of their pregnancy.

Cardinal Symptoms and Physical Findings.—In the pre-eclamptic group 18.9 per cent complained of headaches, 31.1 per cent of ankle edema, 5.9 per cent of epigastric pain, 10.7 per cent of visual disturbances, and albuminuria of varying degree was found in 67.2 per cent. These findings were markedly

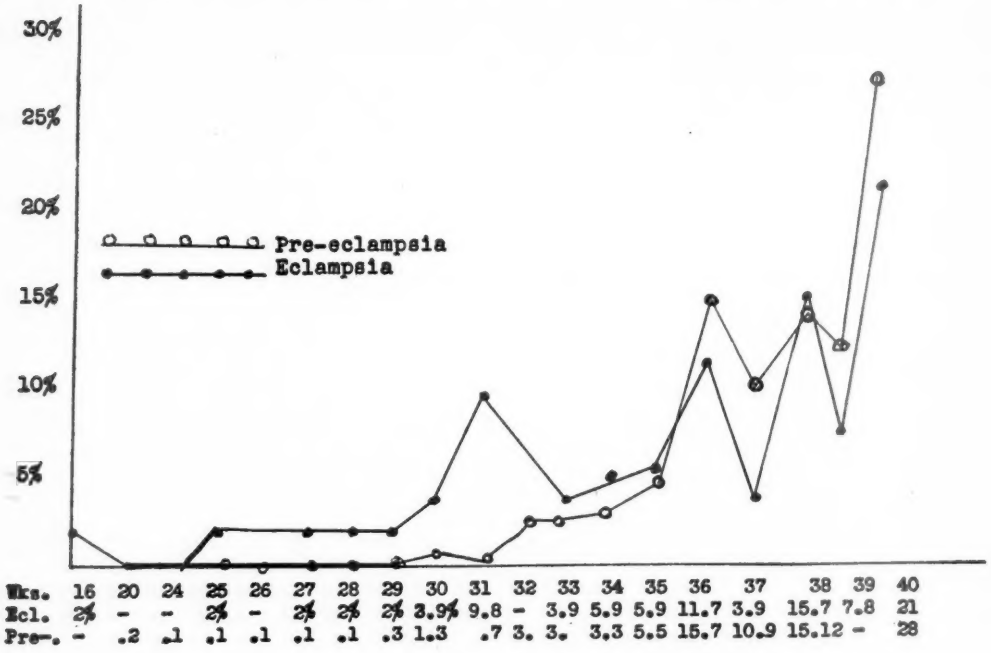

Fig. 1.—Week of appearance of elevated blood pressure.

TABLE III

	PRE-ECLAMPSIA		ECLAMPSIA				HYPER-TENSIVE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Height, inches	1154	63.4	45	63.6	12	62.5	250	63.4
Age, years	1450	27.8	51	27.2	12	27.6	281	32.3
Normal weight, lbs.	1303	137.5	41	127.9	11	132.8	265	152.2
Weight gain to onset of elevation of blood pressure	1295	26.0	41	27.4	---	---	---	---
Headaches	275	18.9	36	72.0	9	75.0	61	21.6
Ankle edema	452	31.1	35	70.0	9	75.0	84	29.6
Epigastric pain	85	5.9	16	32.0	2	16.6	7	2.5
Visual disturbances	156	10.7	23	46.0	7	58.3	26	9.1
Albuminuria	930	67.2	49	98.0	12	100.0	160	58.8
Vertigo	-	-	-	-	-	-	14	4.9
Casts (average)	?		?		12	100.0	?	

elevated in the eclamptic group which showed headaches in 72 per cent, ankle edema in 70 per cent, epigastric pain in 32 per cent, visual disturbances 46 per cent, and albuminuria in 98 per cent. Had the urine specimen been obtained at the proper time, probably all cases of postpartum eclampsia would have demonstrated albuminuria. In the nephritic group, 75 per cent complained of headaches, 75 per cent of ankle edema, 16.6 per cent of epigastric pain, 58.3 per cent of visual disturbances, and 100 per cent had albuminuria and casts. In the hypertensive group headaches were present in 21.6 per cent, ankle edema in 29.6 per cent, epigastric pain in 2.5 per cent, visual disturbances in 9.1 per cent, albuminuria in 58.8 per cent, and vertigo in 4.9 per cent.

Treatment.—The first line of Table IV represents the percentage of patients in this series admitted to the hospital before labor, and their average stay in days before labor began. The remainder of Table IV is a summary of the treatment used over the fifteen-year period. The percentages for magnesium sulfate include both the saturated solution given as a saline cathartic and the concentrated solution given parenterally, even though the action is different. Our present treatment may be summarized as follows:

TABLE IV

TREATMENT	PRE-ECLAMPSIA		ECLAMPSIA		NEPHRITIS		HYPERTENSIVE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Patients admitted hospital average number days	4.75	30.1	7.7	50.9	20.3	66.6	6.7	30.7
Ammonium chloride	108	7.4	2	3.9	0	0	14	4.9
Sedation	551	37.9	38	74.5	10	83.3	132	46.6
Magnesium sulfate	288	19.8	33	64.7	5	41.6	180	63.6
Hypertonic fluids	37	2.5	25	49.0	----------		12	4.2
Diet: L.P.S.F.	661	45.5	36	70.5	7	58.3	166	58.6
H.P.S.F.	48	3.3	–	–	–	–	–	–
N.P.S.F.	22	1.5	–	–	–	–	–	–
Milk	13	0.9	–	–	–	–	–	–

1. All normal patients are given a 1,800 calorie diet made up of 85 Gm. of protein, 75 Gm. of fat, and 200 Gm. of carbohydrate. (These figures are obtained from the diet being used at the Chicago Lying-in Clinic.)

2. Institution of a salt free 85 Gm. protein diet, sedation and enteric coated tablets of ammonium chloride in 1½ to 6 Gm. doses daily if the pressure begins to rise and is accompanied by a sudden increase of weight.

3. Absolute bed rest in the hospital if the pressure remains over 140/90.

4. Hypertonic glucose in water, sedation, and parenteral magnesium sulphate therapy are used in amounts commensurate with the severity of the toxemia. For the eclamptic severe medical management is used. If the pregnancy must be terminated because of failure to respond to medical management, and the cervix is in a state not suitable for delivery from below, cesarean section is performed under local anesthesia. In the nephritic and hypertensive patient, the usual medical management is carried out by the internist, and is augmented by rest that varies from slight restriction of household duties to absolute bed rest in the hospital throughout the pregnancy, depending upon the severity of the symptoms. The abbreviations in the last line under the heading of diet indicate low protein, high protein, and normal protein salt free diets.

Labor and Delivery.—(Table V.) Blood pressure was found to be elevated at the time of labor in 91.6 per cent of the pre-eclamptic group, and in 94 per

cent of the eclamptic group. The absence of elevated blood pressure in 6 per cent of the latter may be explained on the basis of postpartum convulsions. Duration of the first and second stages of labor in primiparas varied from thirteen to sixteen hours. The nephritis group averaged only 5.1 hours; but since only three cases were averaged, this figure may be disregarded.

TABLE V

	PRE-ECLAMPSIA		ECLAMPSIA		NEPHRITIS		HYPERTENSIVE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Elevated blood pressure at labor	1317	91.6	47	94.0	12	100.0	283	100.0
Labor in primipara in hours	717	16.1	30	13.4	3	5.1	65	14.3
Labor: Spontaneous	1358	95.1	32	82.0	8	80.0	263	93.9
Induced	70	4.9	7	18.0	2	20.0	17	6.1
Castor oil and quinine	46	65.7	3	42.8	1	50.0	5	29.4
Ruptured membranes	9	12.8	1	14.3	–	–	5	29.4
Bag	11	15.7	3	42.8	1	50.0	7	41.2
Bougie	4	5.8	–	–	–	–	–	–
Gestation: 40 or more weeks	1138	78.2	20	39.2	6	50.0	183	64.6
Gestation: Less than 40 weeks	316	21.8	31	60.8	6	50.0	91V	32.2*
	5 N.V.	–	1 N.V.	–	1 N.V.		9N.V.	3.2
Delivery:‡ Spontaneous	1155	77.4	24	43.6	8	66.7	247	89.2
Operative	339	22.6	31	56.4	4	33.3	30	10.8

*These figures represent percentages of cases of induced labor.
†V represents cases of sufficient gestation for viability.
‡This is for infants delivered, *not* mothers.

Onset of labor was spontaneous in 95 per cent of the pre-eclamptics, 82 per cent of the eclamptics, 80 per cent of the nephritics, and 94 per cent of the hypertensives. The different methods of induction are enumerated. Castor oil and quinine method was efficacious only if the cervix was effaced and the uterus ready to begin labor. Stripping and rupturing the membranes was much more efficient in inducing labor when the cervix was effaced and the uterus irritable. The employment of bags is not as frequently used as in former years, but it is felt that it still has its place in certain cases. The bougie as a method of inducing labor was used in four cases during the first few years that the hospital was opened. It has not been used since that time.

Length of Gestation.—Forty or more weeks of gestation was reached by 78 per cent of the pre-eclamptics, 39 per cent of the eclamptics, 50 per cent of the nephritics, and 65 per cent of the hypertensive cases. Of those patients who did not reach forty weeks of gestation, there were five pre-eclamptics, one eclamptic, one nephritic, and nine hypertensives that did not reach thirty weeks. All of the infants born of this latter group were stillborn, and all but one weighed less than 1,000 grams.

Delivery.—This was by spontaneous means in 77 per cent of the infants born of pre-eclamptic mothers, 44 per cent of the infants in the eclamptic group, 67 per cent of the infants in the nephritis group, and 89 per cent of the infants in the hypertensive group. The different types of operative delivery will be mentioned later.

Size of the Infants.—(Table VI.) The average weight of the infants in each group was 3,277 Gm. in the pre-eclamptic, 2,781 Gm. in the eclamptic, 2,860

Gm. in the nephritic, and 3,269 Gm. in the hypertensive. The small size of the infant born of the eclamptic and nephritic mother has been observed by nearly all obstetricians.

Stillborn and Neonatal Deaths.—For the pre-eclamptic this incidence was 3.1 per cent and 1.5 per cent; for the eclamptic, 18.1 per cent and 7.2 per cent; for the nephritic, 33.3 per cent and 8.3 per cent; and for the hypertensive 4.7 per cent and 1.4 per cent. A fetal salvage of only seven out of twelve infants born of the nephritic mothers shows the seriousness of this complication as far as the infant is concerned, to say nothing of its injurious effect to the mother.

Twins.—Only in the hypertensive group was the normal ratio of 1:86 pregnancies approximated. In this group the ratio was 1:94. In the pre-eclamptic and eclamptic groups, the incidence was markedly increased being 1:36 for the former and 1:13 for the latter.

Maternal Deaths.—There were five maternal deaths in the pre-eclamptic group for a percentage incidence of 0.34 per cent. Four of the 51 eclamptic mothers died for an incidence of 7.86 per cent. One case or 8.3 per cent of the nephritic mothers died. There were no deaths in the hypertensive group; but five of these 283 cases developed cardiac decompensation, two of which were accompanied by hydrothorax, and one of which was an acute pulmonary edema.

Table VII shows the breakdown of the maternal deaths. By means of early ambulation and other methods that will prevent thrombus formation, it is hoped that the incidence of pulmonary embolism will be lowered. The case of ruptured uterus and shock was one of a transverse presentation that was mismanaged. The case of bowel obstruction and peritonitis can be explained on the basis of trauma to the bowel resulting from some overzealous individual's attempt to express a retained placenta through a closed cervix. The figures at the bottom of Table VII represent the incidence of maternal deaths in cases associated with elevated blood pressure. For the fifteen-year period this was 1:2,826 mothers. Broken down into five-year periods, this was 1:1,489 for 1931 to 1935; 1:5,041 for 1936 to 1940; and 1:7,755 for 1941 to 1945.

TABLE VI

	PRE-ECLAMPSIA		ECLAMPSIA		NEPHRITIS		HYPERTENSIVE	
Weight of baby	1475	3277 Gm. 7.2 lb.	51	2781 Gm. 6.1 lb.	10	2860 Gm. 6.3 lb.	273	3269 Gm. 7.2 lb.
Stillborn	47	3.1%	10	18.1%	4	33.3%	13	4.7%
Neonatal death	23	1.5%	4	7.2%	1	8.3%	4	1.4%
Twins r:ratio	40	1:36.4r	4	1:13r	–	–	3	1:94r
Maternal deaths	5	0.34%	4	7.86%	1	8.3%	0	0.0
Cardiac decompensation	–	–	–	–	–	–	5	1.8%
Hydrothorax	–	–	–	–	–	–	2	
Acute pulmonary edema	–	–	–	–	–	–	1	

Operative Deliveries.—These figures listed in Table VIII represent percentages of the infants delivered by operative means. The percentage incidence of operative delivery was shown in Figure 5 and was 23 per cent for the pre-eclamptic group; 56 per cent for the eclamptic; 33 per cent for the nephritic, and 11 per cent for the hypertensive. Prior to 1942, prophylactic forceps were not employed. Since that time, the general policy of the hospital has been the use of prophylactic forceps; and low or mid-forceps are used when the second stage has reached two hours in primiparas, or one hour in multiparas, or if an indication for immediate delivery arises. Only the low cervical type of cesarean section has been employed during the last three years. Version and extraction

were done chiefly for delivery of the second twin. Table IX shows some of the other indications for sections. Elderly primiparity is not considered a primary indication. One case of placenta previa, two cases of abruptio, four cases of previous section for disproportion, and nine cases of primary disproportion were sectioned because of these complications, and not because of the associated hypertension. Thus the toxemia was the primary indication for 25 of the 41 patients sectioned.

TABLE VII

	MATERNAL DEATHS
Eclampsia	4 cases
Nephritis	1 case nephritis with edema pneumonia and empyema thyroiditis
Pre-eclampsia	5 cases (a) pulmonary embolism 2 cases (b) ruptured uterus and shock (c) ventricular hemorrhage (d) bowel obstruction, resection, and peritonitis
Incidence: 1:2826 1931 to 1935, 7 cases, 1:1489 1936 to 1940, 2 cases, 1:5041 1941 to 1945, 1 case, 1:7755	

TABLE VIII. OPERATIVE DELIVERIES

	PRE-ECLAMPSIA		ECLAMPSIA		NEPHRITIS		HYPERTENSIVE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Low and prop. forceps	209	61.8	9	29.0	1	25.0	17	56.7
Midforceps	51	15.0	5	16.0	–	–	4	13.3
Breech extraction	31	9.2	3	10.0	–	–	6	20.0
Version and extraction	23	6.8	2	7.5	1	25.0	–	–
Cesarean section	24	7.1	12*	38.0	2	50.0	3	10.0
Low cervical	14	–	–	–	–	–	–	–
Classical	10	–	12	–	2	–	3	–
Pubiotomy	1	0.2	–	–	–	–	–	–
Total	339		31		4		30	

*One case of posthumous section.

TABLE IX. CESAREAN SECTIONS (41 CASES)

Low cervical 10	Classical 31	Eclampsia 12	Pre-eclampsia 24	Nephritis 2	Hypertensive 3	
		Placenta previa 1	Abruptio 2	Previous section 4	Disproportion 13	Elderly primipara 3

Time of convulsions.—Convulsions occurred ante partum in 35 per cent, intra partum 33 per cent, and post partum in 31 per cent of the 51 cases of eclampsia presented.

Discussion

During the fifteen-year period that has been reviewed, the maternal death rate has continued to improve at the Lewis Maternity Hospital. Since some of our deaths were preventable, we are still striving to reach the ideal goal. This

improvement in maternal mortality has been the result of various factors, viz., registration of the patients in the early months of their pregnancy; close observation by the attending staff during the patient's pregnancy, labor, and puerperium; institution of treatment when symptoms of toxemia first appear; and individualization of each case, with constant re-evaluation of her physical status while she is under the hospital's management. Table X shows a comparison of the cases at the Chicago Lying-in Hospital and the Lewis Memorial Maternity Hospital. These figures were obtained from a paper read before this society by Davis and Gready[1] in February, 1945, and cover a period from 1931 to 1944. The incidence of convulsive toxemia was 0.18 per cent in both institutions. However, our maternal mortality rate at Lewis was 3.3 per cent higher. The maternal mortality rate from all causes is almost identical in each institution.

TABLE X

	CHICAGO LYING-IN	LEWIS MEMORIAL MATERNITY
PERIOD	1931-1944	1931-1945 INCL.
TOTAL CASES	47,945	28,263
Eclampsia		
Cases	86	51
Per cent	0.18	0.18
Deaths	4	4
Mortality, per cent	4.6	7.9
Total maternal deaths	81	50
Mortality, per cent	0.17	0.176
Per 10,000 mothers	17.0	17.6

The statistics presented are almost all self-explanatory, and further discussion will be limited to only a few subjects.

Although an attempt is made to control excessive weight gain in all patients, it is the patient that shows a sudden increase during the last trimester that causes the greatest concern. This sudden gain is usually due to water retention. The other three most common causes of excessive but gradual weight gain during pregnancy are (1) the person of large stature who had purposely kept herself underweight by eating an inadequate diet, (2) the individual who develops an endocrine obesity, and (3) those who eat too much.

The incidence of ankle edema was tabulated because it is the symptom that the patient first notices. Patients having hypostatic congestion of the venous vessels, and patients during extremely warm weather may have this complaint also.

Epigastric pain in the hypertensive group is probably on the basis of passive congestion of the liver and splanchnic circulation. When present, early cardiac decompensation should be suspected. When present in the pre-eclamptic patient, it usually means that convulsions are imminent.

However, all symptoms, physical findings, and laboratory findings serve merely as gauges registering the degree of the underlying toxemia. Treatment of the symptoms and not the underlying cause is comparable to breaking the thermometer on the dashboard when the engine is overheating.

The absence of maternal deaths in our series of hypertensive cases does not detract from the seriousness of this complication. Acute pulmonary edema is

a medical emergency that demands immediate and adequate therapy to prevent loss of life. With adequate rest, which may mean absolute bed rest for the last two or three months of gestation, these patients can usually be safely carried to term.

Summary and Conclusions

1. Eighteen hundred cases of elevated blood pressure during pregnancy have been presented.

2. The teaching of the importance of adequate pre-natal care in order to detect symptoms of impending toxemia at their first appearance cannot be overemphasized.

3. Prevention of eclampsia is of paramount importance, since the maternal and fetal mortality rises in direct proportion.

4. Nephritis and pregnancy are poor cohorts, as the maternal risk is high and the fetal salvage is low.

5. The incidence of twins in pre-eclamptic and eclamptic toxemias is found to be increased.

Reference

1. Davis, M. E., and Gready, T. G.: Am. J. Obst. & Gynec. 51: 492, 1946.

Discussion

DR. W. J. DIECKMANN.—Findings reported are essentially the same as most investigators have found. The essayists used only an elevated blood pressure as their differential point. I wish to know why they did not use edema and albuminuria in addition.

I do not think diagnoses should be based on just the hospital stay. They should be deferred for at least four months, better six months, or even longer. The ideal is after another pregnancy.

Does the fetal mortality include all pregnancies or only those who went to term? We find that many toxemic patients abort in early pregnancy.

Our incidence of toxemia has not decreased during the last ten years. However, we do have eclampsia almost eliminated, having at the most one case per year. We have very few severe pre-eclamptics. The only ones that we now see are either the patient that has not been under care or has not been into the clinic for a number of weeks.

Since 1933 I have used the concept that patients who develop hypertension early in pregnancy or who develop it late in pregnancy without any abnormal weight gain and little or no edema or in whom the systolic blood pressure is over 200 have an essential hypertension. We have recently completed a follow-up of 600 patients who had two or more pregnancies in our hospital, the first of which was complicated by toxemia. Thirty-seven per cent had a recurrence of toxemia in the next pregnancy, and in these same patients three years later 51 per cent had a recurrence. As more time elapsed the incidence of recurrent toxemia and of hypertension increased progressively.

In some 1,700 toxemic patients we found that 42 per cent had pre-eclampsia or eclampsia, 53 per cent had hypertensive disease, 3 per cent glomerulonephritis, and 3 per cent nephrosclerosis in hypertensive patients. The authors had only 1 per cent hypertensive disease, which I think is far too low.

Dr. Dillon mentioned that it is not so much the amount of weight gained as it is the excessive amounts that the patient is gaining while under observation.

As the doctors in the clinic become more experienced watching for excessive weight gain, for increases in systolic blood pressure, our results in the treatment of these toxemic patients improve. The patients are put under dietary control and bed rest at an earlier date. They are hospitalized when they either do not cooperate or when their condition does

not seem to improve with ambulatory treatment. They may be hospitalized several times in the pregnancy. Any time after 32 weeks, which we consider the period of viability, the pregnancy is terminated if the signs or symptoms warrant it. After 36 weeks we are guided by the severity of the toxemia and the condition of the cervix as determined by vaginal examination. If the cervix is soft and dilated, we rupture the membranes. If there is no dilatation, we may continue medical management in the hospital for a period of five to ten days, examining the patient periodically and, as soon as there is some dilatation, the membranes are ruptured. In most instances, cesarean section for toxemia is an admission that either the patient did not cooperate or that treatment in the clinic or in the hospital was not instituted early enough and intensively enough. We believe it is better to perform a cesarean section under local anesthesia in the pre-eclamptic patient who is having symptoms along with signs (severe toxemia) than to wait until that patient has eclampsia or fetal death or an abruptio placenta.

DR. DILLON Closing).—In answer to Dr. Dieckmann's question, blood pressure was not taken as the sole factor in deciding which were the pre-eclamptics. All of these records were reviewed, and many were reclassified. In some cases this was difficult because of registration at the clinic late in pregnancy, and failure to have adequate follow-up. Our follow-up has been much better in the past few years; and it has been left out with the idea of presenting that in a separate paper at a later date. In the opening portion of the paper, I mentioned that the pre-eclamptic group would include some hypertensives. Had the follow-up been adequate, or had the patients registered in the first trimester, I am certain the incidence of pre-eclampsia would be less, and of hypertension greater.

These figures did not include cases of early abortion. For some reason, we were not seeing these cases. They were evidently going elsewhere. There were some cases of late abortion.

The low incidence of demonstrable edema may have been a result of failure to record its presence on the prenatal record. It is only in the last three years of this study that *all* patients with a pressure over 140/90 are admitted to the hospital, and a complete history and physical done. Some of the eclamptics made their first appearance at the hospital at term, and in a convulsive state in the first years of the hospital's operation. There was one multipara, a gravida iii, para ii, who had convulsions in her first pregnancy, then a normal pregnancy, and then eclampsia in her third pregnancy.

ANTICOAGULATION THERAPY WITH HEPARIN/PITKIN MENSTRUUM IN THROMBO-EMBOLIC DISEASE COMPLICATING THE PUERPERIUM AND GYNECOLOGIC SURGERY*

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DURING the past three years or more, 251 patients with venous thrombo-embolic disease received subcutaneous heparin in the Pitkin menstruum with gratifying results.[1-5] Fifty-three of these 251 subjects were obstetric or gynecologic patients. In view of this rather extensive experience, it seemed opportune to report our results with heparin/Pitkin menstruum in the treatment of thromboembolism complicating the puerperium and gynecologic surgery.

Clinical Material

Most of the 53 patients (Table I) in this study were referred to the Thrombo-embolic Disease Unit by the Gynecological and Obstetrical Department of the Jewish Hospital.†

TABLE I. HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF 53 PATIENTS WITH THROMBO-EMBOLIC DISEASE COMPLICATING THE PUERPERIUM AND GYNECOLOGICAL SURGERY

CLASSIFICATION	NUMBER OF PATIENTS	NUMBER OF PATIENTS WITH PULMONARY EMBOLIZATION	DEATHS DUE TO PULMONARY EMBOLIZATION
Prepartum thrombophlebitis	1	0	0
Postpartum thrombophlebitis	29	7	0
Postoperative thrombophlebitis and/or phlebothrombosis			
Cesarean section	4	1	1
Hysterectomy	15	9	0
Vaginal Plastic	4	1	0
Totals	53	18	1 (1.8%)

Thirty-four of these 53 patients were obstetric, and 19 presented gynecologic problems. One of the 34 parturients received the treatment for phlegmasia alba dolens which developed forty-eight hours prior to the onset of labor; the therapy was interrupted during the actual labor and restarted in the postpartum period. Of the remaining 33 parturients, 29 were delivered vaginally and 4 by cesarean section. Eight of the parturients embolized prior to therapy, in two instances despite femoral vein ligation. Two patients were dicoumarol failures prior to inaugurating subcutaneous heparin/Pitkin menstruum therapy.

Manifestations of thrombo-embolism were present in 19 postoperative gynecologic cases; 15 following abdominal hysterectomy and 4 following vaginal plastic procedures. Ten in this group had one or more pulmonary emboli prior to the heparin therapy; in four patients despite vein ligation.

*Presented in part at a meeting of the Brooklyn Gynecological Society, Oct. 11, 1946.

†We wish to thank the Department of Obstetrics and Gynecology for referring this clinical material.

Treatment Program

The treatment program which follows was that adopted for venous thromboembolism as previously reported.[2-5]

Formulae for Clinical Use.—The ampules* for clinical use (Table II) are as follows:

Heparin/Pitkin Menstruum (V. C.)
ampules, 2. c.c.—each ampule containing 200 mg. heparin sodium salt with vasoconstrictors.
ampules, 3 c.c.—each ampule containing 300 mg. heparin sodium salt with vasoconstrictors.
Heparin/Pitkin Menstruum (Plain)
ampules, 2 c.c.—each ampule containing 200 mg. heparin sodium salt; no vasoconstrictors.
ampules, 3 c.c.—each ampule containing 300 mg. heparin sodium salt; no vasoconstrictors.

Dosage Plan.—In general, body weight and individual reactivity dictate the amount of heparin/pitkin menstruum to be used in a given case. For the initial injection, body weight may be used as a guide. Patients weighing up to approximately 150 pounds (67.8 Kg.) should be given an initial dose of 300 mg. of heparin sodium salt, patients over this weight should be given an initial dose of 400 mg. Subsequently, the dosage should be adjusted according to the intensity of the "heparin effect" as estimated by the coagulation time. Compared with a normal coagulation time of nine to fifteen minutes (Lee-White modification of Howell's method), a coagulation time of thirty to sixty minutes is considered an adequate "heparin effect." In actual practice it will be found that a conventional dose of 300 mg. of heparin will suffice for about 90 per cent of subjects who are normal reactors. The remaining 10 per cent are either hypo- or hyper-reactors requiring 400 or 200 mg. dosages respectively.

Method of Administration.—1. Warm the ampule gently by either holding it under running hot tap water, or immersing in a container of hot tap water until the contents become fluid.

2. Shake thoroughly to disperse any precipitated material.

TABLE II. HEPARIN/PITKIN MENSTRUUM FORMULAS

	WITH VASOCONSTRICTORS		WITHOUT VASOCONSTRICTORS	
Heparin, sodium salt, mg.	300.0	200.0	300.0	200.0
Epinephrine hydrochloride, mg.	1.0	1.0	0	0
Ephedrine sulfate, mg.	25.0	25.0	0	0
Chlorobutanol, mg.	0.5	0.5	0.5	0.5
Eucupin dihydrochloride, mg.	1.0	1.0	1.0	1.0
Pitkin menstruum, c.c.	3.0	2.0	3.0	2.0

3. Draw the contents of the ampule into a dry, sterile 5 c.c. or 10 c.c. syringe, using a sterile needle, gauge 18 (2-inch length). After the contents have been drawn up, the 18-gauge needle should be replaced by a 20-gauge needle for the actual injection.

4. Inject the contents immediately into the deep subcutaneous (or superficial intramuscular) tissue, preferably in the anterior or lateral aspect of the thigh. When subsequent injections are required, use the right and left thighs alternately and avoid sites of previous injection. Do not inject into sites where pressure may be exerted upon the injection area.

*Prepared and distributed by William R. Warner & Co., Inc., New York.

5. Be certain that the contents of the syringe are not too hot prior to the injection. The syringe and contents should feel only slightly warm.

6. Do not apply either heat or cold to areas of deposition unless for purposes of accelerating or retarding release of the drug.

Clinical Use.—In the average case use the entire contents of one 3 c.c. ampule containing 300 mg. of heparin sodium salt. This dose should be sufficient to keep the patient "heparinized" for approximately two days (Fig. 1). Therefore, administer the contents of one 3 c.c. ampule every second day throughout the requisite period of heparinization. If the patient receives a blood transfusion during the period of heparinization, administer the contents of one 3 c.c. ampule immediately following the transfusion, irrespective of when or how many previous deposits have been given. If, for any reason, there is need to stop the effect of heparinization, this can be accomplished immediately by the intravenous administration of 250 to 500 c.c. of whole blood or bank blood not more than three days old.

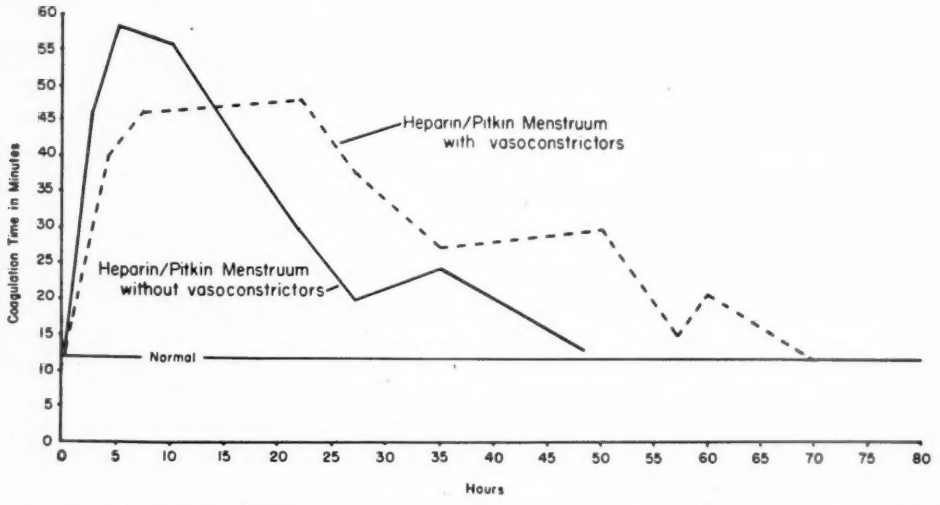

Fig. 1.—Coagulograms; demonstrating average prolongation of coagulation time following the administration of 300 mg. of heparin/Pitkin menstruum.

Method of Following the Patient's Clinical Course.—The effect of heparin is judged by and based on determination of the blood coagulation time which should be estimated daily throughout the period of heparinization. The capillary tube method is inaccurate and should not be used. The Lee-White modification of Howell's method for determination of blood coagulation time is recommended. The technique of performing and estimating coagulation time is as follows:

1. Place four chemically clean, dry 75 by 10 mm. test tubes in a rack.

2. With a sterile, dry syringe and needle, withdraw about 2 c.c. of venous blood from the subject. The test is timed from the moment the blood is first observed in the syringe. Remove the needle from the syringe.

3. Gently distribute approximately 0.5 c.c. of blood into each test tube. Discard the last air-containing fraction.

4. All glassware, syringes, and needles must be absolutely dry. Moisture, alcohol, etc., invalidate the determination.

5. The vein must be negotiated cleanly. If difficulty is encountered, it is best to use a fresh needle and syringe. Even a small amount of tissue juice aspirated into the syringe will give a false result.

6. Once the blood is placed in the test tubes, they must be disturbed as little as possible while observing for the end point. It will be noticed that well-heparinized blood will sediment very rapidly. The tubes should not be shaken after sedimentation of the blood. Look for clotting in the red cell layer as well as in the plasma layer, by gently tilting the tubes. In unclotted blood the red cell layer will flow as the tube is angled.

7. First, gently tilt one tube and note the flow of the red cell layer. If the flow is rapid, discard the tube and wait about five minutes before the second tube is angled. In this way the end point may be approximated, and then finally accurately determined from the third or fourth tube. Once any of the tubes are disturbed, they should be discarded.

8. The patient's coagulation time should be determined before heparinization for control purposes. After that the coagulation time should be estimated daily (twenty-four hours after the heparin injection and immediately before the next heparin injection).

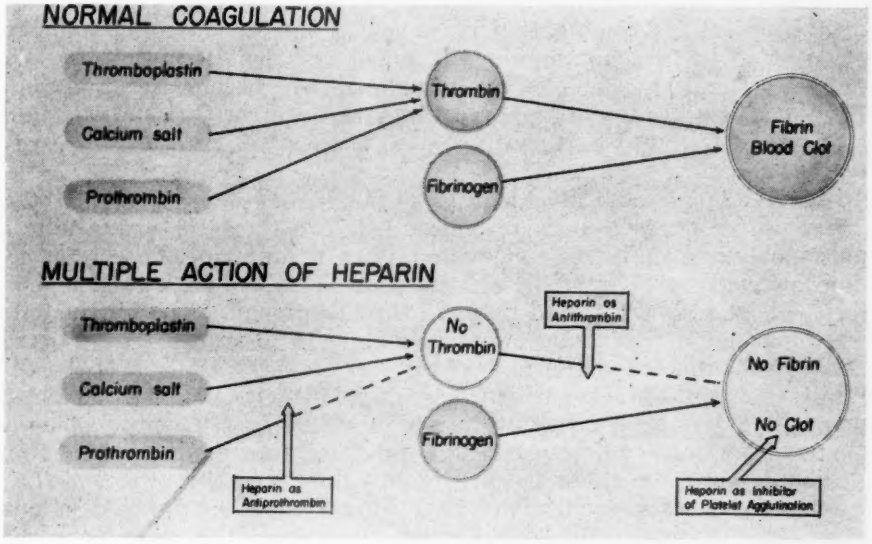

Fig. 2.—Mechanism of anticoagulant action of heparin.

Reactions, Complications in the Use of Heparin/Pitkin Menstruum.—1. The local pain, swelling, and tenderness of the earlier preparations is ascribable to the precipitate which was found to be a combination of heparin and eucupin. The pain factor induced by this precipitate was at times excessive but could be controlled by careful buffering so that the pH of the gel is more physiologically acceptable, and the tendency to precipitation noted in the original ampules is overcome. Other side-effects of the heparin/Pitkin menstruum preparations are trivial.[6] On rare occasions some oozing will occur from the needle puncture. In the several thousand deposits that have been made in over 400 patients with various thrombotic disorders, there was but one instance of hematoma of sufficient proportion to justify interruption of heparinization in a patient with postpartum thrombophlebitis. The patient made an uneventful recovery.

2. Following the administration of a dose of 200 mg. or 300 mg. of heparin sodium salt combined with vasoconstrictor drugs, the patient will occasionally complain of palpitation and nervousness. These reactions require no treatment and disappear within a short time.

3. Digitalis is said to inhibit the anticoagulant action of heparin. If possible, avoid the use of this drug during period of heparinization.

4. If suspension of heparin activity is desired, small transfusions of whole blood or relatively fresh bank blood will inactivate any circulating heparin. An ice bag to the site of deposit, or a tourniquet above it will suspend or slow up the absorption of the drug. In our experience the use of protamine for abrupt interruption of heparinization has not been necessary.

5. In hypertensive patients or those with myocardial disease, it is preferable, although not mandatory, to use heparin without vasoconstrictor drugs in order to avoid the transitory subjective vasoconstrictor effects.

Suggestions for Treatment.—1. In cases of thrombophlebitis, it is advisable to inject the heparin into the thigh which is normal. Avoid using the affected thigh for deposition of heparin until the swelling has partially receded.

2. For hyperreactors employ the 2 c.c. ampule which contains 200 mg. of heparin sodium salt. For hyporeactors administer 400 mg. This is accomplished by combining two 2 c.c. ampules each containing 200 mg. of heparin sodium salt. Where vasoconstrictors are indicated use only one ampule with vasoconstrictors in the combination inasmuch as the amount of vasoconstrictor drugs contained in the one ampule will suffice for the entire dose of heparin.

3. As a general rule for effective heparinization the blood coagulation time should be not less than two to three times the control coagulation time, i.e., thirty to forty-five minutes as contrasted with a control time of nine to fifteen minutes.

Adjuvant Therapy.—Coincident with the institution of heparin therapy the liberal use of papaverine is recommended, 1 to 3 grains every four hours intramuscularly or even intravenously and, later, maintenance dosages by mouth. Smoking is strictly prohibited. Paravertebral block, although used extensively in arterial occlusions, is not used by us in thrombophlebitis as a routine measure since we have found that venous spasm disappears promptly following administration of subcutaneous heparin.

While the addition of antibiotics and/or sulfonamides to the treatment program is not discouraged, these are not necessary in the management of the usual type of thrombo-embolism encountered in obstetric and gynecologic practice. Should, however, there be any identifiable infective etiology, the antibiotic and/or chemotherapeutic program should then be pursued intensively consistent with the nature of the infective organism. The mere presence of a febrile reaction does not connote bacterial invasion and may well be attributable to the mere presence of intravascular thrombosis particularly when the blood clot engages the vessel wall and precipitates an inflammatory intimal reaction.

Results

The clinical deportment of heparin/Pitkin menstruum has been observed in 53 patients (Table I) representing all forms of venous thrombo-embolic disease encountered in obstetrical and gynecologic practice.

The span of treatment for uncomplicated thrombophlebitis and/or phlebothrombosis was ten days to two weeks. For patients with pulmonary embolization, an additional week or two of therapy was required depending upon the extent of pulmonary infarction. In any event, the full heparin effect was present when the patient was first allowed out of bed.

The results in this series were satisfactory as judged by effective control of pulmonary embolization, marked amelioration of pain and discomfort, rapid recession of edema, reduction in morbidity, acceleration in convalescence, and virtual absence of residual edema, particularly when patients were treated without delay.

Most informative are the statistics with respect to the patients who had pulmonary embolization. There were 18 patients in this group with but one fatality, representing 1.8 per cent of the entire series of 53 patients and 5.5 per cent of the 18 patients who had suffered from one or more episodes of pulmonary embolization.

The treatment failure followed sequential femoral vein ligation for recurrent pulmonary embolization incidental to phlebothrombosis following operation for premature separation of the placenta. Subcutaneous heparin was discontinued prematurely two days after the initial left femoral ligation because the pulmonary findings were attributed to virus pneumonia, which was prevalent at the time. The right femoral vein was ligated about ten days after the left femoral vein ligation. Lethal massive pulmonary embolization ensued on the third day following the right femoral vein ligation. Necropsy disclosed old adherent thrombi in the left iliac and left hypogastric veins which were probably the source of the emboli found occluding the right pulmonary artery and main branch of the left lower lobe.

This fatality, the only one in this group of gynecologic and obstetric patients, must be catalogued as a treatment failure for both vein ligation with thrombectomy and supplemental subcutaneous heparin therapy, although the latter was suspended after much too short a span of treatment.

One of the obstetric patients suffered a hematoma at the site of one of the injections which did not interfere with the progress of the treatment program, the patient making an uneventful recovery. In this patient, as in all the other patients treated in the early stages of the disease, the hospital stay was definitely curtailed and the disfigurement eliminated or significantly reduced.

Discussion

The incidence of thrombo-embolic disease varies considerably with individual clinics. A representative statistical review of 6,114 gynecologic operations done at the Breslau Woman's Clinic disclosed 134 (0.19 per cent) cases of thrombo-embolic disease.[7] There were 26 fatal embolic cases in this group, with an incidence of 0.42 per cent. A similar study of 10,297 obstetric cases, including 973 premature labors and abortions, revealed 102 (0.98 per cent) thromboembolic cases. In this group there were six fatal emboli, an incidence of 0.05 per cent. The Maternal Welfare Committee of Kings County recorded 395,655 deliveries from 1938 through 1945.* There were 794 maternal deaths in this group, of which 89 (8.9 per cent) were embolic. This represents one maternal death in 4,400 deliveries, and an average of 11 embolic deaths for each year of the report.

A detailed discussion of the functional pathology and etiology of venous thrombo-embolism is beyond the scope of this report. A comprehensive review of experimental studies and clinical observations in connection with this problem has been presented in previous publications.[1-5, 8] Where a cause may operate to produce thrombophlebitis and/or phlebothrombosis, it should be elicited and removed whenever possible.

Despite early ambulation in the postoperative and postpartum patient, there is an irreducible occurrence of venous thrombo-embolism.[9, 10] The widespread routine use of anticoagulation therapy in the prospective surgical and obstetric patient, while ideal, is not practical or feasible at present. As a result

*Personal communication.

we have expended a great deal of time and effort in an endeavor to detect the potential clotter, the thrombophiliac. A straw in the wind is the report by Morrison, Richter, and Loewe on blood platelet clustering.[11] The report deals with the method and interpretation of a proposed clustering test. Clustering and/or increase in numbers of platelets is directly proportional to their coagulability. The most obvious characteristic of the blood platelet is its clustering propensity.[12, 13] A simple routine blood platelet clustering test was devised as a means of establishing the coagulative status of individuals in comparative health and in disease. In a study of 200 subjects, a correlation between this test and thrombo-embolism was indicated. Its value as a means of detecting the clusterer, the thrombophiliac, and potential clotter, was suggested. The presumptive thrombophiliac and potential clotter identified by blood smear may then conceivably be protected by proper anticoagulation measures during pregnancy and infections prior to anesthesia and pre- and postoperatively. Clinical and experimental investigations of the role of blood platelet clustering in health and disease is being pursued.

While the use of anticoagulants preoperatively is not generally advocated at present, its prepartum use has been suggested in recent reports.[14, 15] Our own related experience with heparin/Pitkin menstruum in the obstetric wards may well suggest its ultimate adoption as a prophylactic prepartum measure. A brief review of this experience has already been presented.

The routine use of anticoagulation therapy as a prophylactic measure must await further clinical and experimental investigation. Many methods of treatment of thrombophlebitis and/or phlebothrombosis have been proposed, although two major thoughts have dominated the clinical scene during the past five years; namely, vein ligation and anticoagulation therapy.

In the past, medical therapy in the form of sedation, rest, elevation, and mobilization of the offending limb has only caused long and permanent disability and, to say the least, anxiety to the clinician. The latter could only hope and meditate that his patient would not embolize. When the latter did occur a fatal outcome was often inevitable.

The Ochsner-DeBakey treatment[16] of thrombo-embolism with paravertebral block reduces the pain by relief of vasospasm. Repeated blocks are necessary but the over-all length of disability and permanent disfigurement are not necessarily lessened. Papper and Imber[17] have recently presented evidence that the use of paravertebral block may be so effective in producing vasodilatation that thrombi may be liberated with resultant embolism.

While our contrary views on the matter of vein ligation have been set forth elsewhere[3-5] the literature abounds in articles advocating this form of therapy for venous thrombo-embolism.

The surgical approach to the problem of venous thrombo-embolism centers around ligation of the deep femoral veins, iliac veins, ovarian veins, or the inferior vena cava. Bilateral femoral vein ligation must be practiced, inasmuch as with unilateral vein ligation, fatal pulmonary emboli may derive from an unsuspected thrombotic process on the contralateral side. Even this procedure,

the magnitude of which is unduly minimized by present observers, does not offer absolute protection against embolization. Allen, Linton, and Donaldson report six deaths due to emboli subsequent to femoral vein ligation in a series of 1,300 patients.[9] There are, furthermore, known fatalities in which the offending embolus originated from the profunda femoris vein proximal to the site of ligation of the superficial femoral vein. Ligation of the inferior vena cava upon a critically ill patient carries a high mortality.[18] Nurnberg[19] collected 526 cases of inferior vena cava ligation for puerperal sepsis with a mortality of 50.7 per cent. Since the favorite site for thrombophlebitis in the parturient and the postoperative gynecologic patient is situated in the venous plexuses about the uterus, adnexa, and pelvic veins, ligation below the femoral veins does not obliterate the focus. Finally, operative procedures which interrupt not only venous but also lymphatic channels contribute considerably to the production of edema. Ligation of the iliacs and inferior vena cava is frequently attended by late complications, permanent lymphedema of the lower extremities and neurovascular changes.

In view of the complications of the surgical approach in the treatment of thrombo-embolic disease, it is apparent that the anticoagulants assume prime importance. Anticoagulation therapy deals with the abnormal physiology of blood and lymph in the body. Of the anticoagulants dicoumarol and heparin have been the most widely used.

Recourse to dicoumarol is understandable because it can be administered orally. The effectiveness of the drug, however, is tempered by the difficulty in planning dosage schedules and, more important, because of its dangerous complications.[20-24] There is great variability in the response to dicoumarol, this lack of uniformity of response being present even in the same individual. Fixed dosage schedules cannot be established; patients must be individualized. The action of dicoumarol is slow, from forty-eight to seventy-two hours being required before its therapeutic effectiveness is achieved. This delay in action is due to the fact that dicoumarol's anticoagulation action is a reflection of its attack on the liver inhibiting the formation of prothrombin.

Due to delay in action and the variability of the patient's response, dicoumarol is not always useful in the early critical stages of thrombosis or major pulmonary embolism where prompt anticoagulation effect is imperative. The delayed action and prolongation in effect after cessation of therapy are disadvantages during or shortly after operative procedures and in patients with anticipated, threatened, or actual hemorrhage. Instances have been observed in which embolism, thromboses, or progression of existing venous thromboses have occurred despite low blood prothrombins induced by dicoumarol.[22] Patients receiving dicoumarol require daily prothrombin determinations. The use of dicoumarol should not be countenanced unless there are proper laboratory facilities for prothrombin determinations by acceptable techniques. The latter are time consuming and relatively expensive.

In the presence of liver disease the use of dicoumarol is contraindicated. It has been attended by irreversible hemorrhage and death.[23] Transfusions of

fresh blood alone do not arrest the hemorrhagic tendency occasioned by the drug. Massive dosages of vitamin K are required which may, in turn, reinduce thrombosis.[24]

In summary then, the delayed action, potential hazards, the unpredictable treatment failures, and the requisite complicated but indispensable laboratory procedures militate against dicoumarol as the anticoagulant of choice.

The properties of heparin which render it uniquely applicable in thromboembolic disease may briefly be enumerated; it prevents, with the aid of a plasma co-factor, the conversion of prothrombin to thrombin; it forms with serum albumin a strong antithrombin; and, finally, it prevents the formation of thromboplastin from platelets.[25] The accepted knowledge concerning the mechanism of the action of heparin is graphically portrayed in Fig. 2.

According to Jorpes[26] heparin is a mucoitine polysulfuric acid. The most potent preparations of heparin contain 45 per cent of sulfuric acid which results in an exceedingly strong negative electric charge. No other compound of high molecular weight in the mammalian body has such a strong electric charge. Apparently, heparin exerts its action through this charge. This seems to be supported by the neutralizing effect of basic protamine, which has the property of promptly counteracting the action of heparin. The multiple effect of heparin on thromboplastin, prothrombin, thrombin, the hemolytic complement, iso-hemagglutinins, and different enzymes is most readily explained as a loading and unloading of electric charges on the proteins concerned. The properties of heparin predicate the fact that a clot, regardless of its site or stage, cannot propagate in the presence of heparin. However, what happens to the clot which is already present?

It has been possible to determine experimentally in animals at what stage of clot formation heparin administration results in solution of the clot and what effect heparin has on the organized clot.[4, 8]

Briefly, studies on the effect of heparin in experimental venous thrombosis in the rabbit have yielded the following data:

1. Red cell clots not organized and containing a minute amount of fibrin (sludge stage) disappear completely under heparin therapy.

2. Heparin therapy maintains patent adjacent collaterals and tributaries which ordinarily would become involved in the thrombotic occlusive process. These compensatory collaterals often become as large as the originally occluded vessel. This phenomenon has not been observed in control animals. It may be assumed, though not necessarily proved, that these processes also occur in obstructed lymphatics.

Until recently the routine use of heparin has been limited by the expense, by the huge amount of drug required in the individual case, and by the cumbersome method of administration which requires a continuous venoclysis or repeated daily intravenous dosage. The restriction of motion of the patient, the almost absolute certainty that superficial angiitis would eventually occur at the site of injection, and the haphazard control of the clotting time rendered heparin therapy useless unless constant untiring supervision were available.

In an attempt to achieve prolonged absorption of heparin, pellet and capsule implantation in experimental animals was attempted. Erratic, unpredictable effects were observed. However, a slower and more equable distribution of heparin was obtained by incorporation of the drug in the Pitkin menstruum developed to regulate the rate of release of water soluble drugs injected intramuscularly or subcutaneously.[1, 2]

The ingredients of the pitkin menstruum are gelatin—15 to 30 per cent, dextrose—5 to 12 per cent, glacial acetic acid—0.5 per cent, and sufficient distilled water to make 100 per cent. The rate of liberation of the contained heparin is inversely proportional to the viscosity of the menstruum; the optimum percentage of gelatin and dextrose were found to be 18 and 8 per cent, respectively, for the preparation containing heparin. The technique for the use of the heparin/Pitkin menstruum preparation has already been considered.

For optimum results heparin therapy should be inaugurated as early as possible. The advantages of preventing spread of thrombosis before it can give rise to pulmonary embolism or serious local damage are obvious, and has been stressed repeatedly in the literature.[27] Admittedly, thrombo-embolism may be a treacherous and unpredictable condition; at times it occurs catastrophically and without warning. Nevertheless, if one is alert for slight premonitory signs, these will be discovered more often than has been supposed. One such diagnostic sign, described by Allen,[28] is an inexplicable rise in the pulse, temperature, and respiration at the same reading or observation. Where, after operation, these have shown the normal downward course, any fresh rise, however small, after the fourth or fifth day, must always evoke suspicion. Another sign sometimes observed is an unaccountable feeling of disquietude and restlessness which affects the patient. Or she may state, perhaps not until questioned, that she was kept awake during the night by a faint ache and a feeling of cramp in one of the calves, so-called "charley horse," a symptom which may already have disappeared. Complaint of even a slight stitch or pain in the chest must arouse strong suspicion of pulmonary infarction which is confirmed if the patient develops an irritative cough or expectorates blood-streaked sputum.

If any of these general signs are noted, a detailed physical examination must be made to elicit the cause. Examination consists of palpation of the groins, inner aspect of the thighs, popliteal spaces, the calves, and the veins of the feet, looking for swelling and tender areas. Conspicuous signs need not necessarily be present. In early cases one may note only slight swelling of the lower leg, an increased glossiness and tension of the skin, a faintly cyanotic discoloration in comparison with the other leg, and prominence of the superficial veins of one leg as compared with the other. All these signs need not necessarily be present but, if one or more of them is observed, the probability of an incipient thrombosis is considerably increased.

The most important sign is direct tenderness in the calf, discovered by pressure with the palpating fingers. Such tenderness will be more significant if none is elicited when the muscles at the same level are compressed from side to side. An increase in the consistency of the muscular part of the calf is another customary feature of thrombosis. Finally, the foot is brought into dorsal

flexion and, if pain is induced (Homans sign) it is very significant of deep venous thrombosis. Because of the difficulty of establishing the normal standard, we have abandoned the routine clinical use of phlebography.[29]

It is evident from a critical review of our series of patients that a comprehensive trial of subcutaneous heparin in the Pitkin menstruum has been carried out with good results. While other expedients, such as sulfonamides and penicillin, may be used in conjunction with it, heparin alone in clinically established thrombophlebitis, irrespective of etiology, is attended with consistent, beneficial, if not dramatic results. These include diminution of temperature, pain, and swelling which often become manifest within a few hours after initiation of therapy. This improvement is predicated on the limitation in the progress of the formed thrombus, while the original inflammation expends itself, and the thrombus either resolves or becomes organized. Since there is no further actual propagation of thrombus, there is a rapid and marked diminution in vasospasm. In all cases, morbidity is lessened and convalescence accelerated. It is felt that prolonged, deforming, and incapacitating edemas are further prevented in these patients by keeping lymphatics patent.

As has been described earlier, the general systemic anticoagulation effect of heparin seems to us to be a more rational therapeutic weapon than local vein ligation, especially when the precipitating cause of thrombosis is not yet known and the initiating site of thrombosis can be ascertained in many cases only by vague and indeterminate clinical signs.

Summary and Conclusions

1. Experimental investigation and clinical observation indicate that heparin plays a vital role in arresting the progress of intravascular thrombosis and promotes restoration of the vascular stream. It also enhances collateralization.

2. Two hundred fifty-one patients with various forms of venous thromboembolic disease have been treated with heparin/pitkin menstruum. This series included 53 subjects who were obstetric or gynecologic patients. Thirty-four of these 53 patients were obstetric, and 19 presented gynecologic problems.

3. The treatment of venous thrombo-embolic disease with subcutaneous heparin in the Pitkin menstruum was attended with lessened morbidity, prompt and rapid clinical improvement, and little or no residual edema. The causative factors responsible for the one treatment failure have been analyzed. Treatment failures with other methods have subsequently ended in recovery following the routine administration of the heparin/Pitkin menstruum preparation.

4. As a result of observations of its clinical deportment, the subcutaneous administration of heparin in the Pitkin menstruum is recommended as a safe, simple, practical, and effective method for anticoagulation therapy in thromboembolic disease complicating the puerperium and gynecologic surgery.

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CANCER; EVOLUTIONARY REVERSION IN CELL METABOLISM

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IT IS proposed that cancer is essentially a reversion in cell evolution resulting from an abortive attempt of the regenerating cell to adapt itself to an environment that is deficient in one or more of the elements essential for the formation of the enzyme pattern it requires to become a fully differentiated specialized cell. *Recent studies have revealed a marked similarity in the enzyme patterns of embryonic and malignant cells.* There is also evidence to suggest that certain chronic low grade tissue vitamin deficiencies which result in impaired function of the normal adult cell, shift the metabolic balance in favor of the growth and development of a cell with an embryonic cell enzyme pattern. Growing cells must synthesize their vitamin containing enzymes from available constituents in their immediate environment. When the cell environment is marginally deficient, the relatively low concentration of one or more of these essential elements may not permit the synthesis of the usual adult cell enzyme systems, and yet may be entirely adequate for the synthesis of the enzyme pattern of an embryonic cell. When, in the face of such deficiency conditions, local tissue growth is continually forced in the repair response to a chronic irritant, the regenerating cells, if they are to survive, are forced to revert to the use of their embryonic cell enzyme pattern. It is suggested that when these factors, (a) chronic nutritional deficiency, marginal in character, and (b) continuously forced local tissue growth, obtain over a long period, the newly formed regenerating cells will by gradual stages revert morphologically as well as enzymatically and finally, after many cell divisions (cell generations), assume all of the behavior characteristics of the primitive embryonic cell.

Speculation on the possibility that malignant tumors are analagous to embryonic tissue goes far back to the earliest theories of cancer. It is only recently that experimental data supporting this idea have been forthcoming.

It has been shown by Burk,[1] and again by Greenstein and Thompson[2] in comparative studies on fetal rat liver, adult liver, and hepatoma that, metabolically, the malignant tissue closely resembles the embryonic in the extent of glycolysis, the activity of a number of different enzyme systems and in sulfur distribution. In these respects the fetal and *malignant* tissue are similar and differ significantly from the adult tissue. West and Woglom[3] have shown the same paralellism between the biotin content of embryonic and malignant tissues. In some embryonic tissues the biotin content is higher than in the adult tissue, in others lower. They found "In all cases the biotin content of both tumor and embryo tissues deviated in the same direction from the corresponding normal." There was no evidence from their experimental work, however, that tumor growth was in any way dependent on biotin. Considering the similarity in their enzyme patterns, embryonic and malignant tissues must

also coincide in their comparative content of certain other B vitamins. Burk[1] and Greenstein and Thompson,[2] in studies on liver tissue referred to above, have shown that many of the riboflavin containing enzymes are found in much lower concentrations in tumor and embryonic tissue than in the normal adult tissue. Robertson and Kahler,[4] by assays on rat tissue, have presented actual data on the riboflavin content of fetal liver as compared to normal adult, normal regenerating liver, and hepatomas induced by various carcinogenic agents. With the riboflavin concentration of normal adult liver as standard at 100, regenerating liver also had a value of 100, fetal liver –19, and six hepatomas varied from 16 to 47. It is, therefore, evident that in the rat the tumor and embryonic tissue resemble one another in their content of riboflavin and contain considerably lower concentrations of this essential element than the corresponding normal adult tissue. Barnes,[5] in studies of the cord blood, maternal blood, and placenta in human subjects, found that the concentration of thiamine in the cord blood is almost invariably lower than that in the maternal blood; and that placental tissue has a very low value for the concentration of thiamine. This suggests that the fetal embryonic enzyme pattern depends, again, upon a lower concentration of this B-factor.

In addition to the similarities in their enzyme patterns, many other resemblances between malignant and embryonic tissues have been noted. Morphologically, the similarities are striking; and their behavior characteristics are similar (both are rapidly growing tissues, and both can be heterologously transplanted). These resemblances strongly suggest that malignant tumors are formed from cells which have resumed certain embryonic characteristics in a disordered growth process.

One feature in these similarities which may be particularly significant is the fact that the enzyme systems of both embryonic and malignant tissues in comparison to those of adult tissues are apparently much less dependent on certain essential components of the B-complex which the regenerating cell must obtain from the constituents available in its immediate environment.

General body growth stops when any one essential component of new cells is not available. Focal growth activity, however, as a necessary part of the repair response to the stimulation of a chronic irritant, is forced under the pressure of the demand for new cells as important protective elements. According to the degree of the deficiency focal growth activity will be affected in different ways; when severe, no growth activity will take place regardless of the pressure of the demands of the repair process. However, if the deficiency is marginal, the chronic repair stimulus being continuous, the tissue may make an effort to form a supply of new protective cells from the limited materials available. In this action it must undergo an adaptation process and produce a cell which can survive in the "deficiency" environment. The results of studies on the enzyme systems of embryonic cells referred to above indicate that these cells can function adequately with lower concentration of certain B vitamins than the corresponding normal adult cell. A marginal deficiency for the adult cell would not be a deficiency state for the embryonic cell. In the adaptation process, therefore, an embryonic type of cell must be produced. This evolutionary reversion which has been conditioned by the local tissue response to a stimulus to regeneration in a marginal deficiency

cell environment we regard as the *possible* initiating factor in the malignant process in many cancer producing tissues.

Evidence suggesting that marginal deficiency conditions and chronic inflammation are almost invariably associated with the development of one type of cancer in human subjects has been presented by one of us (J. E. A.).[6] In a survey of 100 gynecologic patients, 50 with early uterine cervical cancer and 50 controls, chronic dietary deficiency was present in 90 per cent of the cancer patients according to both the dietary-history standard and the measure of thiamine excretion. Almost all showed evidence of chronic cervicitis. Evidence of similar nutritional status was found in only 10 per cent of the controls. This same dietary inadequacy, chronic in character and marginal in degree, associated with chronic inflammation, was also found in a high percentage of another group recently reported[7] who had not yet developed malignant disease but exhibited evidence of morphologic changes typical of "precancer" in the cells scraped from the squamocolumnar junction of the cervix.

The role of vitamins in enzymology and their relation to malignant disease has been the subject of many recent studies. Those which have been shown to be actual components of the enzyme equipment of the fully differentiated cell appear to be vitally related to the process of carcinogenesis. Certain members of the B group of vitamins, particularly riboflavin, niacin, and thiamine, are especially implicated.

The studies of Kensler and co-workers,[8] elucidating the prominent role played by riboflavin in the protection of rats against hepatoma formation while on a diet containing p-dimethylaminoazobenzine, are outstanding in this field. Pollack and Taylor and associates[9] have made an invaluable contribution to cancer research by compiling data on the vitamin content of normal adult and malignant tissues. They have shown that malignant tissues resemble one another in their content of various B-factors; and differ from the corresponding normal adult tissues in that their enzyme systems appear to require lower concentrations of riboflavin,[9] thiamine,[10] and niacin.[11] The similarities between embryonic and malignant tissues have been pointed out, and evidence indicating that the enzyme pattern of the embryonic cell, like the malignant cell, depends on relatively low concentrations of riboflavin and thiamine has been reviewed. Others have investigated vitamin metabolism and its relation to malignant disease in man. Martin and Koop[12] and Abels and associates[13] have shown a close association to be present between intra-oral cancers, precancerous oral leucoplakia, and B-complex deficiencies. Studies on uterine cancer showing the close association between this form of malignant disease and the existence of a chronic subclinical thiamine deficiency have been referred to above.[6, 14]

The effects of a chronic hypovitaminosis on the cell tissue environment might be analyzed as follows: As a result of the deficiency the function of the fully differentiated cell is hampered because of an interference with certain of its enzyme systems. It is able to continue but a labored existence. On the other hand, all of the essential requirements of the embryonic cell, whose growth and efficient functioning apparently depend on lower concentrations of some of the B-vitamins, may be fully complied with. The sugges-

tion is that when these conditions are present at a focus of chronic irritation where cell division, in the process of repair and regeneration, is occurring repeatedly, eventually the regenerating cell will be forced to undergo a process of adaptation and will revert to the cell type which can function efficiently under the restricted conditions imposed. In the process of adaptation the cell, in effect, undergoes evolution in reverse and resumes after many cell divisions its embryonic characteristics. Once embryonic reversion has taken place, growth and invasion may occur under the influence of continued malnutrition or in response to various body growth hormones which have a selective stimulating effect on the tissue involved.

In studies on uterine cervical cancer,[6] evidence has been presented suggesting that these three factors: nutritional deficiency, chronic infection, and hormonal stimulation, are important in the genesis of this malignant disease. Interpreting this evidence as applicable to carcinomatous disease in general and considering the many resemblances between malignant and embryonic tissues which have been demonstrated, three essentials in carcinogenesis might be described as follows:

1. The existence of a focus of chronic irritation where cell division as a part of the process of regeneration and repair is occurring repeatedly and as a body defense reaction must continue as best it can in spite of the nutritional environment.

2. A tissue vitamin deficiency that alters the cell environment making it impossible for the new cell formed in the process of regeneration to complete the enzyme equipment of the fully differentiated cell, but at the same time adequately fulfilling all of the metabolic requirements of an embryonic cell. These two factors operating over a long period cause the cell to undergo reversion and assume its embryonic characteristics.

3. A hormonal factor which acts upon the cell which has assumed its embryonic character enzymatically and morphologically and stimulates its further development, growth, and invasiveness.

I. Chronic Irritation

The importance of chronic irritation, mechanical or infectious, as a significant factor in the development of malignancy has long been recognized. As a focalizing factor it may have its effect in a number of ways. As a site at which continuous cell division is occurring it is the point at which cell changes conditioned by environmental factors will take place. As an area of hyperemia it will be an area that is subjected to increased amounts of any hormonal agent present in the blood stream. There is also suggestive evidence that inflamed cells or cells adjacent to an inflamed area are able to fix certain hormonal agents and thus cause a marked increase in their local concentration. This evidence has been reviewed and discussed in a previous publication.[6]

The concept suggested implies that some stimulus to cell division is absolutely necessary. This is in accord with the fact that malignant disease most commonly develops at sites of chronic irritation or in organs such as the female

mammary gland and those of the female generative tract where activities run in a physiologic cycle involving recurrent episodes of massive desquamation followed by rapid regeneration of tissue.

II. Tissue Vitamin Deficiency

Kensler and associates[8] have shown that in the production of liver cancer with p-dimethylaminoazobenzine, in addition to cell destruction and a resultant repair response, there is an interference with an enzyme system—the enzyme system in which Coenzyme I is concerned. Riboflavin is essential for the efficient performance of Coenzyme I. One surmises that as a result of the interference with this enzyme system the usual metabolism of the regenerating cell is impossible. It loses the ability to perform many of its highly specialized functions and is forced to depend for its survival on other of its enzyme systems. These are presumably adequate for reproduction and growth, but lacking the total enzyme pattern of the fully differentiated cell, the new cell also lacks its highly specialized functional capacity. It is a cell which is adequate for more primitive functions only, viz., reproduction and growth. Its enzyme pattern is now so fashioned that all of the materials which enter the cell are used for growth and reproduction. It is a malignant cell. Riboflavin in large doses plus casein, or an adequate diet, will enable Coenzyme I to function properly in the regenerating cell and will almost completely annul the carcinogenic effect of p-dimethylaminoazobenzine. This suggests that one of the important aspects of p-dimethylaminoazobenzine activity as a carcinogenic agent is its effect in creating a relative riboflavin deficiency in an area where active regeneration is taking place; that it creates a relative deficiency of a factor necessary to the regenerating cell for the formation of the full enzyme pattern required for the performance of the specialized tasks of a highly differentiated cell.

Russell[15] has shown that a diet deficient in thiamine and riboflavin will significantly decrease the induction period of tumor formation when the cells of the central nervous system of the rat are subjected to the effects of methylcholanthrene. In summary he states, "It is suggested that the altered metabolism of the cells of the nervous system resulting from the deficiency of thiamine and riboflavin caused the cells to respond more readily to the carcinogen."

There is, therefore, ample evidence that various vitamin factors are directly concerned with the propensity of the cell to become malignant. When deficient, the transformation is more readily effected. The fact that the functional activity of the new cell is not hampered in any way by the low vitamin concentration suggests that it is formed in the adaptation process. It is doubtful whether it is always one particular vitamin factor which is involved. It may at one time be one, at another time another. The essential feature is an interference with the enzymes necessary to the cell for the performance of its highly specialized functions. It has been shown that p-dimethylaminobenzine acts fundamentally in this manner. It is presumed possible, though not proved, that other agents which have been implicated in the production of malignancy may act essentially in the same fashion. The virus responsible for mammary

carcinoma in mice may interfere with these enzymes. Neoplastic-producing x-rays may knock out this set of enzyme systems. It is known that porphyrins interfere with vitamin metabolism and that certain derangements in porphyrin metabolism are associated with some forms of malignancy.

The altered cell possesses the enzyme system of an embryonic cell—a system geared for growth and reproduction. We might then plausibly picture malignant disease as essentially a reversion to an embryonic type of cell metabolism conditioned by a change in cell environment. This change in cell environment results in the inability of the newly formed regenerating cell to complete the enzyme pattern it requires for the specialized functions of a highly differentiated cell. Its more primitive enzyme systems, however, which are adequate for division and growth remain intact. The cell, if it is to survive, is forced to revert enzymatically to the use of these embryonic enzyme systems. A cell that is stimulated in the process of repair and regeneration to repeated division in the deficiency environment will eventually revert morphologically as well as enzymatically to the embryonic state. Thus the malignant process is initiated, a neoplasm is formed. Under the influence of specific growth stimulating body hormones its growth characteristics will be determined. It may immediately assume the rapid growth properties and the invasiveness of a highly malignant growth if there is a potent enough growth stimulus present. On the other hand, the cells so changed may remain for years as a tiny neoplastic focus only to be activated some time later when the body hormonal balance is altered by some additional nutritional factor or by one of the hormonal alterations associated with stress or aging.

III. The Hormonal Agent

There has been considerable controversy as to the status of body hormones, e.g., estrogen, as carcinogenic agents. Being structurally related to the known carcinogens, benzpyrene and dibenzanthracene, the possibility that estrone and estradiol and related compounds possessed carcinogenic properties was readily inferred. Estrogens were shown to increase the frequency of the development of malignancy in the mammary gland and the female tissues of Müllerian duct origin of experimental animals when the other requirements for the development of these malignant growths were present. Estrogens alone, however, except in massive doses and over a prolonged period, would not produce malignant growths. And, as pointed out by Dodds,[16] stilbestrol and hexestrol which do not possess the condensed carbon ring of estrone and the carcinogenic agents, but do possess the gynecogenic properties of estrogens, have the same influence in increasing the frequency of the development of these malignant growths. Therefore, the effect of estrogens in the production of these tumors is probably due purely to the marked growth effect which they exercise selectively on the tissues concerned.

Jensen and Tenenbaum,[17] in a review on hormones and enzymatic reactions, conclude, "It appears that the action of hormones on the rate of enzymatic reactions takes place only in the intact cell. It is known that the activity of certain enzymes is dependent on cellular integrity." If hormones

do not act except upon the intact cell, we suggest that their action may be principally that of altering the permeability of the cell membrane to elements essential for the operation of the cell enzyme systems. A growth promoting hormone may permit essential elements required by the enzyme systems concerned with growth and reproduction to enter the cell. As more of the essential elements are made available, more activity and more growth is possible. While they are excluded the cell's enzyme systems, lacking energy material, remain inactive. Thus the neoplastic cell may remain dormant, its growth potentialities locked within because of the exclusion by the cell membrane of materials essential for growth. With a significant alteration in the body hormonal status a sudden alteration in the cell membrane takes place, materials essential for the operation of its enzyme systems are made available, and its growth potencies suddenly manifest themselves perhaps years after the formation of the neoplastic cell has taken place.

Significant changes in the body hormonal status may occur with age or with changes in the body nutritional status. In the hormonal changes of the climacteric there is often evidence of overactivity of some pituitary hormones as the depressant effect of the gonadal hormones on the pituitary is gradually withdrawn. There may be alterations in the pituitary growth hormone during this period. Nutrition has a marked effect on endocrine function.

Tannenbaum[18] has shown that underfeeding causes a notable reduction in the incidence of mammary gland carcinoma in susceptible strains of mice. It has been pointed out that this effect is in large part, perhaps wholly, due to the secondary effects of caloric intake on endocrine gland activities. The production of estrogens is significantly reduced and the mammary gland is not subjected to the usually strong growth stimulating effect that this hormone exerts. There is evidence also that selective nutritional deficiencies may increase the amount of estrogen in the blood stream. Biskind and Biskind[19] have shown that a B vitamin deficiency may result in impaired hepatic function with a resultant failure of the estrogen inactivation-excretion mechanism. In the patients with uterine malignancy referred to above,[6] accompanying the thiamine deficiency evidence of high endogenous estrogens was consistently present in the character of the cervical cytology.

Inherited characteristics which determine the intensity of endocrine gland activity have an important bearing on the genetic aspects of carcinogenesis. It has been shown that the characteristics of endocrine gland activities as determined by hereditary factors is of significance in determining the susceptibility of certain strains of mice to the development of mammary gland carcinoma. There is, in addition, some unusual property of the nucleus-cytoplasm complex which we might say determines a ready tendency of the cell to undergo evolutionary reversion. This property is inherited and has not yet been explained. The possibility of genetic factors causing a peculiarity in general cell membrane permeability may also be worthy of consideration.

The Cell Enzyme Systems

In the production of hepatomas with p-dimethylaminoazobenzine, an interference with one set of enzymes results in the development of a cell that con-

tains only a part of the enzyme system of the fully differentiated parent cell. This part the liver cell used for growth and reproduction during its embryonic period. The enzymes which the cell in the regenerating phase would ordinarily acquire as it proceeded to differentiation have been kept from it. Occasionally, in the malignant transformation, not all of the specialized systems are interfered with and the cell, e.g., those of some prostatic carcinomas, possesses enzyme properties intermediate between those of an adult and those of an embryonic cell, but in its behavior characteristics it is more closely analogous to the embryonic cell.

In the malignant transformation it is doubtful if the cell ever acquires new enzyme systems, for there is always a loss of functional capacity. It redevelops or re-emphasizes enzymatic potencies already present which are of benefit for immediate survival in the existing environmental conditions. The fact that when the enzyme pattern which enables the differentiated cell to perform its specialized functions is destroyed or lost, the cell takes on the behavior characteristics that the remaining enzyme systems are best fitted to perform is not surprising. This suggests that one of the important mechanisms of internal cell control, keeping growth potencies within the cell in check, is the presence of the "specialized" enzyme systems. It is as if these systems exercised a priority demand on energy material within the cell and "starved" the particular enzyme systems that undertake the activities resulting in growth and reproduction. Once the specialized enzyme systems are interfered with, any food material entering the cell, the amount and character of which may be determined by the action of a hormone on cell membrane permeability, is immediately available for growth and reproduction.

Greenstein and Thompson[20] have pointed out that the enzyme patterns of malignant tissues are remarkably similar both qualitatively and quantitatively, irrespective of their tissue of origin. Taylor, Pollack, and Williams[21] have shown that tumors are remarkably uniform in their B-vitamin content. From this ". . . it is concluded that malignant neoplasms of various types and from various animals tend to have similar cellular metabolism forming in effect a common tissue type." The similarities between malignant and embryonic tissues have been pointed out above. Normal tissues on the other hand vary markedly in their concentration of various enzymes. This appears to be directly related to the variations in function from tissue to tissue.

The thought emerges that possibly all cells, since they have a common origin from a mass of undifferentiated embryonic tissue composed of similar cells, may have a common group of enzymes which form a basic "primitive" group, and, superimposed on these, acquired in the process of differentiation, a second group which varies from tissue to tissue depending on differences in function, making the performance of the cell's highly specialized tasks possible.

Thus we may picture the normal adult cell as containing two groups of enzyme systems. The one common to all cells, embryonic, malignant, or normal adult, which is specific for the requirements of growth and reproduction. The cell depends on these for its regenerative capacities. This group requires but small concentrations of certain of the B-vitamins. The other group de-

velops in the cell as differentiation and specialization of function occur. They vary in concentration from tissue to tissue because of the functional variations from tissue to tissue. They depend upon relatively high concentrations of the B-vitamins for efficient performance. We may plausibly regard this group as a "prepotent" group which exercises a priority on the energy materials that are brought to the cell. Thus while they are intact energy materials are directed toward specialized functional activities and none are available for the secondary more "primitive" group. If the regeneration process results in the formation of cells that are unable to complete this set of enzymes because of cell environment deficiencies, all of the energy materials which are made available to these cells are used for growth and reproduction.

The existence of hypovitaminosis as an isolated fact, however, does not mean that the cell will eventually become malignant. It will probably remain morphologically the same although functionally impaired. However, if a cell which has retained the ability to reproduce itself—still possesses the primitive enzyme group—is confronted with a tissue environment characterized by a hypovitaminosis and is stimulated to repeated cell division, the vitamin deficiency will eventually, over a long period of time, impose a restriction upon the enzyme pattern which the newly formed cell can acquire. This will limit its capacity as a specialized differentiated cell and eventually, we submit, it will by gradual change become dedifferentiated until it has reverted completely to the embryonic form.

Reversion Process—Dallo's Dictum

There is a generally accepted principle in biology regarding the irreversibility of evolution which is known as Dallo's Dictum. It states that, so far as animal structure is concerned, evolution is irreversible but, regarding adaptation to a new environment simulating conditions which obtained in the past in another environment, evolution is reversible. Applying this principle to the regenerating cell confronted with an environment in which there is a deficiency of the elements required for its function as a highly differentiated cell but a plentiful supply of all of the elements required for the function of the capacities it exercised as an embryonic cell in the past it would appear that all of the factors conditioning evolutionary reversion are in operation.

There are a number of facts which appear to indicate that the transformation from a normal to a neoplastic cell is not an abrupt process but rather a gradual transformation involving a series of graded intermediate states. Roskelly and associates[22] in studies on the biochemical changes which take place in this transition, have found that alterations in the cell enzyme pattern begin to appear long before it can be said that the tissue is malignant. The pathologist in his study of biopsy material frequently recognizes morphologic changes which give the cell an appearance intermediate between that of the normal and the neoplastic cell. To these he applies the term "precancerous." In the study of the cervical cytology smears of a large series of gynecologic patients by one of us[7] the "precancer cell-complex" was encountered so frequently as to be considered a significant cytologic entity. As mentioned

above, they were present in the cervical cytology picture of patients who as a rule also showed evidence of a chronic subclinical thiamine deficiency and chronic cervicitis. As one would expect, the process of evolutionary reversion is a gradual one and occurs only after many cell generations (cell divisions). These findings also imply that the atypical morphologic forms seen may be regarded themselves as evidence of chronic hypovitaminosis.

Factors Which Determine Invasion

In general it may be stated that invasion results from a complete breakdown in the mechanism for control of growth potencies within the cell. This may result from either a continuously strong growth stimulus overcoming the cell's natural barriers or from a complete breakdown within the cell with dissolution of the barriers inherent in the cells internal structural organization.

It has been suggested that endocrine growth factors act upon the cell membrane, making it more readily permeable to the selective materials required for the enzyme systems concerned in growth activity. In the absence of the endocrine factor, therefore, the cell membrane would perform an important function in growth control. In rapidly growing anaplastic carcinoma the malignant tissue often takes on the character of a syncitium, nuclei in a mass of cytoplasm. It may be that the loss of cell membrane in such a tissue is one factor in determining its rapid growth characteristics; one of the control barriers has been entirely broken down.

There is evidence to suggest that the enzymes concerned with the specialized functions of the differentiated cell are located in the cytoplasm. It has long been recognized that the function of the nucleus is of prime importance in the processes concerned with growth and reproduction. If the specialized enzymes may be regarded as a "prepotent" group of enzymes which rapidly utilize energy materials which enter the cell for functional purposes none will be available for the nuclear enzyme systems. Thus the growth and reproduction activities of the nucleus will be held in check. A cytoplasm with highly specialized enzyme systems may then be regarded as an additional growth controlling mechanism.

We might then plausibly picture the malignant potencies of a cell as inherent in the normal functions of its nucleus and the highly developed properties for growth and reproduction which reside there. For the exercise of these functions certain materials are required. If they are supplied in ample quantities, growth proceeds at a rapid rate. However, in the normal adult specialized cell the nucleus is starved. These materials are kept from it by two barriers—the surrounding cytoplasm which contains a "prepotent" set of enzyme systems, and the cell membrane. Once the cytoplasmic barrier has been altered by chronic subnutrition, growth activity in the cell is under the influence of cell membrane permeability alone. The total growth potencies of the cell may then be readily provoked by a strong growth promoting endocrine factor.

Once these two growth controlling agencies are broken down, the cells of the neoplastic focus which are supplied with the most nutrient material will

be most active. Thus the cells at the base of the tumor adjacent to the nutrient supply of normal tissue will grow; the tumor will expand and invade the subadjacent normal tissues.

Summary

From facts recently accumulated by various scientific groups and the suggestive evidence presented by a number of clinical investigators, a possible mechanism for the production of malignancy has been postulated. According to the concept outlined, neoplastic cells arise from foci where recurrent cell division is occurring in response to the stimulus to repair and regeneration. Some external factor interferes with the completion of the enzyme pattern of the regenerating cell and prevents it from acquiring the enzyme systems required for the highly specialized functions of the fully differentiated cell. Under these circumstances, in an effort to adapt to its environment the cell is forced to revert to its primitive embryonic enzyme group which can function efficiently under the restricted conditions imposed. This primitive group is especially geared for growth and reproduction. After many cell divisions (cell generations) without the completed enzyme systems, the cell by gradual stages reverts completely and assumes the morphologic and behavior characteristics of a primitive embryonic cell. Much of the activity of such a cell is influenced by various body hormones with specific growth-stimulating properties. There is considerable evidence to suggest that a chronic subclinical vitamin deficiency is one external factor which can affect the regenerating cell in this way. It is possible that various agents, chemical carcinogens, neoplastic-producing x-rays, viruses, and other factors which have been implicated in carcinogenesis may act in essentially this fashion.

It has been recently pointed out by a number of independent authorities[20, 21] that malignant tissues regardless of species origin or of their site of origin within the host, are biochemically so similar as to constitute a common tissue type. Williams,[23] in commenting upon this striking similarity, states: "This remarkable resemblance between cancers, regardless of what animal they arise in, what tissue they come from, or how they are induced, we believe to be a highly important and revealing fact and one which strongly suggests a common etiology."

Some phases of the concept presented in the above are based on suggestive evidence alone, more confirmatory evidence is to be desired. It is, however, presented at this time as the suggestive evidence and confirmed factual findings welded into this interpretation appear to offer a plausible mechanism for the production of various forms of malignant disease while invoking nothing more unusual than the disordered function of the known biologic properties of the individual cell.

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CERVICAL CANCER IN YOUNG GIRLS

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CARCINOMA of the uterine cervix in young girls differs from the disease in adult women in three important respects: its apparently worse prognosis, the preponderance of adenocarcinoma over the epidermoid type, and its extreme rarity. The literature records only four five-year survivals among patients under 21 years of age with cervical cancer (Pollack and Taylor, 1947). In this same age group approximately two-thirds of all carcinomas of the cervix are of the glandular type, in contrast to the relatively low incidence of 5 per cent or less with which this type of cervical cancer appears among older women. So rare is carcinoma of the cervix in minors that such cases constitute gynecologic curiosities.

In a statistical tabulation of 937 deaths from uterine cancer in 1870, Glatter recorded only two patients under the age of 21 years. Gusserow (1886) could not add a single authentic case when he reviewed 3,385 cases of carcinoma of the cervix sixteen years later. The number of acceptable cases still stood at two in 1905 (Steffen). Several cases have been reported in more recent years, however. In the latest review of the literature on carcinoma of the cervix during the first two decades of life, Pollack and Taylor (1947) collected thirty cases and added one of their own, a girl of 18 years, bringing the total to thirty-one cases. The acceptable total may be somewhat less than this, however, for the following reasons. In one instance the same patient has obviously been the subject of two separate reports (MacDonald, 1929; Morse, 1930). In another case (Amesse, 1932) the cervical origin of the tumor is not clear; and in still others, originally thought to be carcinomas, the diagnosis was changed later to endothelioma (Philipp, 1907), teratoma (Adams, 1916), and adenocarcinoma of the fundus (Lockhart, 1935), respectively. On the other hand, occasional cases, such as those of Little (1896), Schreiner and Wehr (1934), and Kelly (1939), apparently have been overlooked. Regardless of the exact number of authentic cases, cervical cancer in girls of 20 years or younger is extraordinarily rare. It is my purpose, therefore, to report two additional cases of carcinoma of the cervix in young girls, one aged 12 years, the other aged 19 years.

CASE 1.—D. C. (R. H. No. 9595), a 12-year-old white schoolgirl, was admitted to the Roosevelt Hospital on April 13, 1920, because of persistent leucorrhea of several months' duration. She had had an appendectomy six weeks previously in another city. A large polypoid, hemorrhagic, friable tumor was discovered involving the anterior lip of the cervix and extending to the anterior vaginal wall. A piece of the tumor was removed for biopsy, the pathologic report being adenocarcinoma of the cervix. The tumor cells were arranged in two ways, some in the form of small irregular acini, but the larger number forming long anastomosing strands, which were supported by thin cores of connective tissue stroma. The cells were large and cylindrical, with faintly staining cytoplasm and oval reticular nuclei (Fig. 1). On April 15, 1920, one hun-

dred milligrams of radium were applied in the cervix for twelve hours. A similar application was made for eight hours on April 24, and the patient was discharged from the hospital on April 27. She was readmitted on June 9 of the same year for another treatment. During the interim she had been symptomatically well and was completely relieved of the vaginal discharge. The cervix appeared much improved, but there was still a slightly rough and nodular area on the right side, extending to the right anterior vaginal wall. On June 11 one hundred milligrams of radium were inserted into the vagina against the cervix for six hours. Another application of 50 mg. of radium for eight hours was made on August 11, bringing the total radium dosage to 3,000 milligram hours. At this time the cervix seemed to be essentially normal except for paracervical induration, which was interpreted as a cicatricial reaction to the previously administered radium. On Oct. 25, 1920, the patient was reported to be suffering with abdominal pain, vomiting, weight loss, and lumps in the groin. She went progressively downhill and died at home on July 7, 1921, fifteen months after treatment was begun.

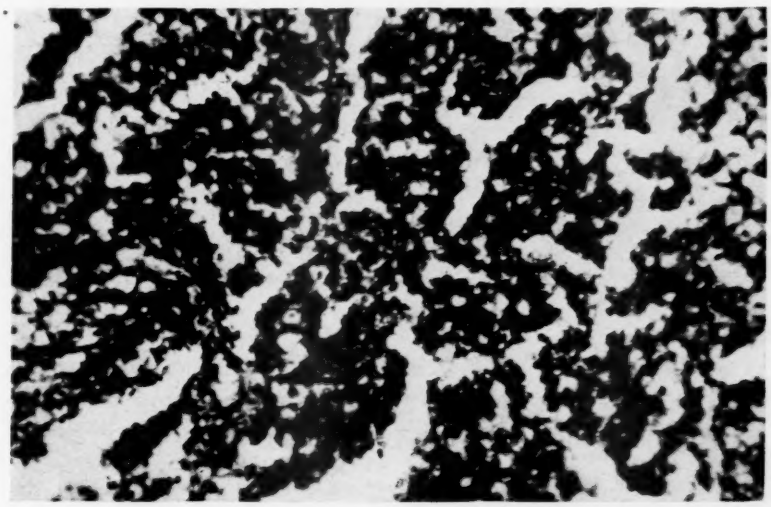

Fig. 1.—Case 1. Adenocarcinoma of cervix in girl aged 12 years.

Case 2.—M. G. (R. H. No. 8225), a 19-year-old single, nulliparous, white Polish office worker, was admitted to the Roosevelt Hospital on Oct. 27, 1918, complaining of vaginal discharge which she had had since her menarche at the age of 9 years; and backache, weakness, and nervousness of three months' duration. Her menses had been profuse and prolonged, the flow coming at intervals of fourteen to twenty-eight days, and lasting for ten days. Her last menstrual period began Oct. 6, 1918. Examination under anesthesia revealed an intact hymen and a soft polypoid mass at the external cervical os. Neither the fundus of the uterus nor the adnexa could be felt. Dilatation and curettage and trachelorrhaphy were performed on October 28. Sections of the cervical tissue showed epidermoid carcinoma of the cervix (Fig. 2); the curettings were diagnosed as "chronic hypertrophic endometritis" (endometrial hyperplasia). On November 27, radical abdominal hysterectomy, bilateral salpingo-oöphorectomy, and appendectomy were carried out. No residual tumor was found in routine sections of the extirpated uterus and cervix. The patient was last seen on Oct. 22, 1919, eleven months after operation, at which time she seemed completely well, had gained 43 pounds, and showed no evidence of tumor recurrence.

Comment

Case 1 is the seventh reported instance of carcinoma of the cervix in girls age 12 or under. Table I shows the salient features of each. The tumor described by MacDonald and by Morse is included as a cervical carcinoma because it was so stated to be, although their reports do not exclude the possibility of its fundal origin. Adenocarcinoma was the histologic type of each of the six tumors for which this feature was recorded.

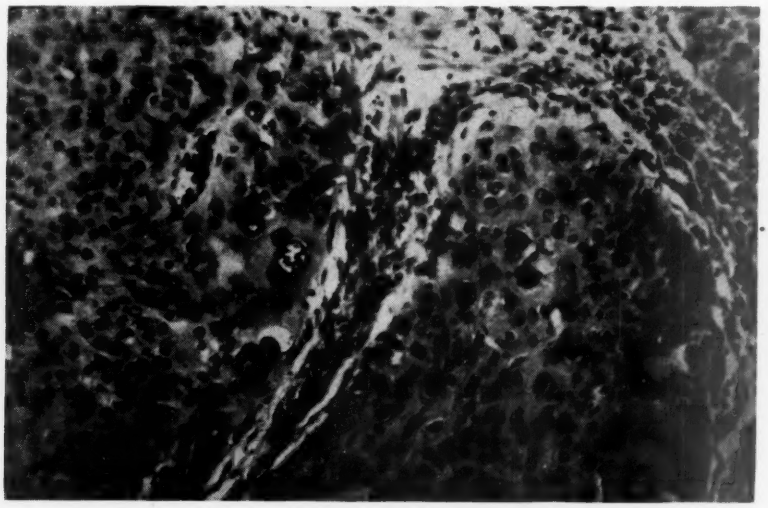

Fig. 2.—Case 2. Epidermoid carcinoma of cervix in a girl aged 19 years.

TABLE I. REPORTED CASES OF CARCINOMA OF CERVIX IN GIRLS AGED 12 YEARS OR UNDER

AUTHOR	YEAR	AGE	TYPE	TREATMENT	SURVIVAL
Ganghofer	1888	8 years	Adenocarcinoma	Excision and cauterization	Died in 2 weeks with variola
Glöckner	1908	7 years	Adenocarcinoma	Laparotomy	No follow-up
Bumm	1909	7 months	Not stated	Laparotomy	No follow-up
Findley	1924	6 months	Adenocarcinoma	Hysterectomy	No follow-up
MacDonald Morse	1929 1930	10 years	Adenocarcinoma	Exploratory; x-ray	Died within a year
Scheffey and Crawford	1932	22 months	Adenocarcinoma	X-ray	Died in 6 weeks
Speert	1947	12 years	Adenocarcinoma	Radium	Died in 15 months

The striking difference in the relative incidence of histologic types of cervical cancer between children and adults has not been explained. The low incidence of cervical carcinoma in general in young girls is not surprising. The phenomenon which requires explanation is the disproportionately lower incidence of epidermoid cancer in children. The juvenile years constitute a period of relative quiescence in the squamous epithelium which lines the vagina and covers the portio of the cervix. A membrane which is normally 20 to 30 cell layers thick in mature women may be only one-fourth or one-fifth this thickness in prepubertal girls. Mitoses are correspondingly less frequent in children. This difference explains the increased susceptibility of the juvenile vaginal membrane to infection and its diminished capacity for repair. Meyer's studies

on the embryology of the vaginal mucosa and lower cervix (Novak, 1944) have shown these parts of the reproductive canal to be of a single origin, namely from the urogenital sinus. The thickness of its surface epithelium is clearly related to estrogenic control. In a similar fashion, hormonal function is believed to be one of the major factors which control the advance or regression of the junction between the stratified squamous epithelium and the columnar epithelium within the cervical canal. In young girls in whom estrogenic activity is at a low and presumably constant level, the line of junction between the two varieties of epithelium within the cervix would be expected to remain relatively static. In mature women, on the other hand, higher estrogenic titers and the fluctuations which result from the menstrual cycles and from pregnancies tend to make the cervical squamocolumnar epithelial junction a region of unrest in which the squamous epithelium now advances, now retreats.

It is precisely at this junction between the zones of squamous and columnar epithelium that most epidermoid cervical cancers originate. The conditions of unrest which might conceivably favor neoplastic development in the squamous epithelium are lacking in prepubertal girls. In Case 2, on the contrary, where the cervical tumor was of the epidermoid type, an associated lesion of the endometrium was found, which is generally regarded as an indication of excessive or unopposed estrogenic stimulation, namely endometrial hyperplasia. Recent studies of vaginal cytology (Ayre, 1947) suggest exactly this type of hormonal aberration as a common concomitant of epidermoid cervical cancer in adults.

The poor prognosis which has been associated with cervical carcinoma in children may be the result of inadequate treatment rather than any specific peculiarity of the disease. This suggestion will be put to test by subsequent cases in which the patient is treated by currently approved techniques of radium and x-ray. Most of the reported cases have occurred before the modern era of radiotherapy. Case 1 represents the only patient in the group under 13 years of age who received the benefit of radium. In the collected series of Pollack and Taylor, only six patients had been treated with radium, the only two authentic five-year cures being among this group.

Summary

1. Two cases of cervical carcinoma are reported in girls aged 12 and 19 years, respectively.

2. This report includes the seventh recorded case of cervical cancer in girls aged 12 years or under. The salient features of these cases are tabulated.

3. In contrast to the preponderance of epidermoid cervical cancer in adult women, adenocarcinoma is the commonest type of cervical carcinoma in young girls. A theoretical explanation for this difference is suggested.

4. The poor prognosis associated with cervical cancer in young girls in the past may be the result of inadequate treatment.

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FACE PRESENTATION*

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OBSTETRIC textbooks give the incidence of face presentation as one in every 200 to 300 deliveries. Posner and Buch[1] reported in 1943 the incidence at Harlem Hospital, New York, as one face presentation among every 529 deliveries. From Jan. 1, 1931, through July 31, 1946, at the Philadelphia Lying-In Hospital there have been 61 face presentations in a total of 35,163 deliveries, or an incidence of one face presentation among every 576 deliveries. The purpose of this paper is an analysis of these 61 cases as to etiology, management, and end results.

Etiology

The causes for face presentation are usually listed as maternal and fetal, and are divided as follows:

A. Maternal causes
   1. Faulty axis of the uterus
      a. Lateral version
      b. Forward position (pendulous abdomen of the high multiparous patient)
   2. Contracted pelvis, or normal pelvis with large baby
   3. Pelvic tumors

B. Fetal Causes
   1. Protrusion of the anterior part of the neck
      a. Several coils of cord around the neck
      b. Enlarged thyroid gland, etc.
   2. Anencephaly and other forms of monstrosities
   3. Dolicocephaly elongation of the occipital arm of the head lever)
   4. Placenta previa

Lateral version of the uterus was not mentioned in any of these cases. Table I shows the parity of the cases and the type of pelvis. There were almost an equal number of primiparous patients and multiparous patients; but almost 60 per cent of the multiparous patients, or 30 per cent of the total patients, had

TABLE I

PARITY	TOTAL	TYPE OF PELVIS		
		GYNECOID	JUSTOMINOR	FLAT
Para i	29	18	9	2
Para ii	13	13	0	0
Para iii	9	7	2	0
Para iv	3	1	2	0
Para v and above	7	4	2	1
Total	61	43	15	3

had two or more children. Of the 29 primiparous patients, there were 11, or 38 per cent, with some form of pelvic abnormality, while of the 32 multiparous patients there were only seven, or 22 per cent, showing pelvic abnormality.

*Presented by invitation at a meeting of the Philadelphia Obstetrical Society.

Table II shows the birth weights of the infants in this series and the incidence of each weight group in patients with adequate or normal pelves. The average birth weight for the infants in this series was 7 pounds, which is slightly below the average birth weight for infants born in this hospital.

TABLE II. INFANT BIRTH WEIGHT

	3 POUNDS OR LESS	3 TO 5½ POUNDS	5½ TO 6 POUNDS	6 TO 7 POUNDS	7 TO 8 POUNDS	8 TO 9 POUNDS	9 TO 10 POUNDS	OVER 10 POUNDS
Total	5	4	2	12	23	9	3	3
Normal pelvis	4	3	1	10	14	8	3	1

One-half of the patients with abnormal pelves gave birth to infants weighing 7 to 8 pounds. Almost 25 per cent of the infants were well above average birth weight, i.e., 8 pounds or more. Only three of these 15 infants weighing 8 pounds or more were born to women with abnormal pelves: one, weighing 8 pounds 10½ ounces, was delivered by internal podalic version and breech extraction of a para vii with a history of previous difficult deliveries and measurements indicating a slightly contracted pelvis; the second, weighing 10 pounds 15¾ ounces, was delivered by internal podalic version and breech extraction with aftercoming head forceps of a para iii with slightly contracted pelvis; and the third, weighing 10 pounds 1 ounce, was delivered by Kerr cesarean section of a para vii with justominor pelvis and a history of previous long and hard labors. Some degree of relative disproportion was probably present not only in these three latter cases, but in all of the cases with large infants. Therefore, instead of only 18 cases of disproportion (i.e., taking pelvic measurements alone as the criterion), there were 30 cases in all with some degree of cephalopelvic disproportion; or almost one-half of the cases showed either small pelvis by measurement or an average pelvis with an oversized infant.

There were no pelvic tumors mentioned in any of the 61 cases. Special search was made through the hospital records of these patients, but none had pelvic tumors recorded either on previous or subsequent hospital admissions.

The cord was around the neck in only one case. Diagnosis of face presentation was made early in labor in this case and confirmed by x-ray. The patient, a 36-year-old para iii, was delivered by classical cesarean section and the cord was found wrapped around the infant's neck three times. There was no incidence of abnormal enlargement of the neck in this series.

The incidence of monstrosities in this series was high. Of the 61 infants, seven, or over 11 per cent, were monstrosities. Five of these infants were anencephalic monsters, while the other two were acraniorachischisis. This figure is somewhat lower than the average given in most texts for the incidence of monstrosities in face presentation.

Actual measurements of the fetal heads were not made in this series. However, no comments were made in any of the cases concerning unusually long heads noticed on routine neonatal examination.

Placenta previa occurred in only one case in this series. Cesarean section was performed in this case and a face presentation was an incidental finding rather than an indication for the cesarean section.

Morbidity and Mortality.—There were no maternal deaths in this series, and the maternal morbidity (using the standard of morbidity as a temperature of 100.4° F. occurring during any two 24-hour periods through the tenth day excluding the first twenty-four hours) was 8.7 per cent. There were five cases of endometritis, one case of pyelitis, and one case of incisional abscess. The history of the latter case illustrates the results of poor obstetric judgment:

M. W., 30-year-old primiparous patient, was admitted to Lying-In Hospital from another institution after having had ruptured membranes for one week and after twenty-one

hours of hard labor. Forceps delivery had been attempted in the other institution resulting in a third degree laceration of the perineal floor. Pelvic measurements taken on admission showed a justominor pelvis, and examination revealed posterior face presentation. The patient was delivered by Porro cesarean section of a stillborn boy weighing 7 pounds 8 ounces. There was a rather stormy postoperative course and an incisional abscess formed. When the abscess was opened and drained the temperature returned to normal. The perineal floor was repaired on the thirteenth postoperative day.

The fetal mortality for face presentation was nearly four times the average fetal mortality for the hospital, but compares favorably with most statistics for face presentation. A total of twelve, or 19.7 per cent, of the babies were either stillborn or died before the tenth day. There were eight, or over 13 per cent, stillbirths and four, or 6.5 per cent, neonatal deaths. This is an uncorrected fetal mortality; of these twelve infant deaths, seven were monstrosities and one was a normal infant weighing less than two pounds. Table III gives the fetal mortality correlated with birth weight. There was 100 per cent mortality among the five infants weighing 3 pounds or less (however, four of these were monstrosities, and the only normal infant weighed 1 pound, 13 ounces). It might be expected that the larger babies would sustain more injuries in delivery, but of the 38 infants weighing over 7 pounds, there was only one stillborn (the case delivered by Porro cesarean section cited previously) and two neonatal deaths, one of which was a monster.

TABLE III. INFANT MORTALITY

	3 POUNDS OR LESS	3 TO 5½ POUNDS	5½ TO 6 POUNDS	6 TO 7 POUNDS	7 TO 8 POUNDS	8 TO 9 POUNDS	9 TO 10 POUNDS	OVER 10 POUNDS
Total No. infants	5	4	2	12	23	9	3	3
Total Mortality	5	1	1	2	1	2	0	0
Stillborn	3	1	1	1	1	0	0	0
Neonatal	2	0	0	1	0	2	0	0
Monsters	4	1	0	1	0	1	0	0

There was mention in most of the cases of the presence of edema and bruising of the face. In addition to these two not uncommon complications there were four infants with evidence of trauma. Table IV correlates the type of delivery with the form of injury. All of these infants improved and were discharged from the hospital in apparently good condition.

TABLE IV

Internal Podalic Version and Breech Extraction
1. Dislocated shoulder
2. Cyanosis, listlessness, and xantochromia of the spinal fluid

Midforceps Rotation and Delivery
1. Traumatic cellulitis of the head

Low Forceps Delivery
1. Cyanosis of the face

Position.—According to most textbooks the incidence of the various positions in face presentation correlates closely with the incidence of the occipital presentation to which it corresponds, i.e., 85 per cent of face presentations are said to be right mentoposterior and left mentoanterior corresponding to left occipitoanterior and right occipitoposterior occipital presentations. However, in this series there was an almost equal distribution among left mentoanterior, right mentoanterior, and left mentoposterior, and right mentoposterior occurred only four times. The position was mentioned on the chart in 57 of the 61 cases. Table V gives the incidence of each position in this series.

TABLE V

	ANTERIOR	TRANSVERSE	POSTERIOR	TOTAL
Left	12	5	13	30
Right	14	5	4	23
Unknown	3	0	1	4

No explanation can be offered for this deviation from the accepted average except the small size of the series. However, it is noticed that Posner and Buch's series also deviated from the expected incidence.

There were two cases of compound presentation involving the hand in this series. No mention was made that the prolapse of the hand was considered to be an etiologic factor in either of these cases.

TABLE VI. MANAGEMENT

	PRIMIPARAS				MULTIPARAS				
TYPE OF DELIVERY	ANTE-RIOR	TRANS-VERSE	POSTE-RIOR	UN-KNOWN	ANTE-RIOR	TRANS-VERSE	POSTE-RIOR	UN-KNOWN	TOTAL
Spontaneous	3	0	2	2	8	3	1	0	19
Low forceps	6	2	3	0	4	0	0	0	15
Midforceps	1	0	0	0	0	0	0	0	1
Low forceps with rotation	0	0	0	0	0	0	1	0	1
Midforceps with rotation	0	2	0	0	0	1	0	0	3
Internal podalic version and breech extraction	1	0	1	0	0	1	2	0	5
Internal podalic version and breech extraction with forceps on aftercoming head	2	0	0	0	2	1	3	1	9
Kerr cesarean	0	0	2	0	2	0	0	0	4
Classical cesarean	0	0	0	1	0	0	2	0	3
Porro cesarean	0	0	1	0	0	0	0	0	1

Type of Delivery.—Table VI gives the method of delivery for this series according to the position of the infant, and separates primiparous patients from multiparous patients. It is interesting to note that 19, or almost one-third, of the patients delivered spontaneously, including two primiparous patients and three multiparous patients with posterior positions, all of which rotated spontaneously. Another 25 per cent of the patients were delivered by forceps without forceps rotation. So there was a total of six posterior and four transverse positions which rotated spontaneously (one transverse was rotated manually and then delivered by low forceps). Internal podalic version and breech extraction was used in almost 25 per cent of the cases; cesarean section was the method of delivery in, eight, or 13 per cent of the cases. Table VII lists the indications for cesarean sections in this series. Two of the sections were done electively before the onset of labor, one with placenta previa as the indication and the other after x-ray diagnosis of face presentation was made. The one Porro cesarean section has been reviewed earlier. The remaining five were done from five to eight hours after the onset of labor. Table VIII gives the fetal mortality

TABLE VII. INDICATIONS FOR CESAREAN SECTION

Cephalopelvic disproportion	5
Malpresentation (face)	2
Placenta previa (face presentation incidental)	1
Total	8

correlated with the type of delivery. It is surprising to note that the more traumatic types of deliveries as forceps rotation and aftercoming head forceps were not associated with any deaths.

TABLE VIII. INFANT MORTALITY VS. TYPE OF DELIVERY

	SPONTANEOUS	LOW FORCEPS	INTERNAL PODALIC VERSION AND BREECH EXTRACTION	CESAREAN
Stillborn				
Premature	0	0	0	0
Term	2	0	0	1
Monsters	1	2	1	0
Neonatal deaths				
Premature	1	0	0	0
Term	0	0	1	0
Monsters	2	1	0	0
Total (normal) infant mortality	3	0	1	1

The average duration of labor for both primiparous and multiparous patients was far below the accepted normals. For the primiparous patients labor varied from one hour, twenty-three minutes (for a 2 pounds 12 ounce infant) to thirty-two hours, thirty-four minutes (for a 2½ pounds anencephalic monster), and the average duration of labor was fourteen hours. In the multiparous patients the length of labor varied from two hours (for a 9 pound infant) to thirty-two hours, fifty-eight minutes (for a 7 pounds 3 ounce infant), and the average duration of labor was eleven hours and thirty-six minutes.

Discussion

Considering each of the commonly accepted etiologic factors for face presentation (and excluding multiparity per se as a factor) only 37 of the cases in this series present a definite cause for the malpresentation:

Abnormal pelvis	18 (1 monster)
Normal pelvis with large infant	12 (1 monster)
Monstrosities (not included above)	5
Placenta previa	1
Cord around the neck	1
	37

Therefore, almost 40 per cent of the cases occurred in women with clinically normal pelves, having normal average or smaller than average infants, and with no complications of etiological value. Whether these patients did have normal pelves can certainly be questioned, and the occurrence of a face presentation in a supposedly normal pelvis would call for a careful check of all measurements at subsequent pregnancies.

According to this small series the prognosis for both the mother and the infant does not seem grave. Although the maternal mortality for the hospital is generally low, the absence of a maternal mortality in this series cannot be disregarded. At first glance an infant mortality of 19.8 per cent seems high; but a corrected figure (excluding monsters and infants under 3 pounds birth weight) of four, or 6.5 per cent, compares favorably with the general average for the hospital for the years included in this series. Two of these four deaths were a result of poor obstetric judgment. The one case was brought in from another institution with a dead baby after attempted forceps delivery; the other

was a neonatal death following internal podalic version and difficult breech extraction in a para vii with a slightly contracted pelvis and history of long labors and difficult deliveries. Well-timed cesarean sections in these two cases, avoiding the traumatic deliveries (or attempted delivery), would undoubtedly have resulted in living healthy infants; and in the first case earlier section would have prevented the necessity for Porro cesarean. The two other infant deaths were due to nonpreventable causes. One case came into the hospital with a dead baby, the cause of antepartum death of the infant could not be determined; the other death was due to compression of an occult prolapse of the cord resulting in intrapartum death of the infant a few hours before delivery.

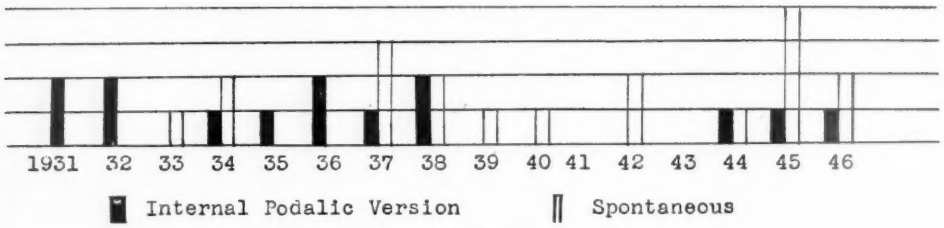

Fig. 1.—Yearly incidence of version.

There has been a definite trend in this hospital toward more conservatism in the treatment of face presentation. The fact that over 50 per cent of the cases delivered spontaneously or with only low forceps proves out the dictum, "If a 'face' is progressing, leave it alone." Fourteen, or almost 25 per cent, of the cases were managed by internal podalic version and breech extraction. This means that over one-half of the cases requiring major operative procedure for delivery were managed by version. Fig. 1 shows the incidence of internal podalic version occurring in each year covered by this paper, and also shows the incidence of spontaneous delivery for the same period. Eleven of the versions were done between 1931 and 1938, inclusive, while only three have been done since 1938. On the other hand, between 1931 and 1938 only eight patients, or 25 per cent, delivered spontaneously, while since 1938 there were eleven, or almost 40 per cent, delivered spontaneously. This parallels the trend of this clinic to do fewer versions.

An incidence of 13 per cent cesarean sections seems high, yet when we consider that only one infant was lost among these eight sections and it was lost because the section was not done early enough, cesarean section for face presentation with any degree of disproportion seems justified. Indeed, if cesarean section had been done in at least one other case (the version and difficult extraction) probably another infant would have been saved. With the maternal mortality and morbidity of cesarean sections decreasing, the value of this procedure as a means of obtaining a living infant is increasing.

Summary

1. A series of 61 face presentations occurring in 35,163 consecutive deliveries in Philadelphia Lying-In Hospital is analyzed.

2. The classification and etiology of this condition are discussed.

3. There were no maternal deaths.

4. There were 12 fetal deaths, however, only four of these deaths occurred in babies normally formed and weighing more than three pounds. Two were due to poor obstetric judgment; one to prolapsed cord; and one to antepartum death, cause unknown.

5. There was a high incidence of monstrosities; five were of the anencephalic type, the other two acraniorachischisis.

6. There was almost equal distribution between left mentoanterior, right mentoanterior, and left mentoposterior position; no explanation for the deviation from the expected incidence is offered.

7. The prognosis for mother and infant is generally good.

8. The majority of patients can be safely delivered spontaneously or by low forceps. Cesarean section proved to be the safest method of delivery in those cases in which disproportion was present. Internal podalic version is not being used as often as in earlier years.

Reference

1. Posner, A. C., and Buch, I. M.: Surg., Gynec. & Obst. **77**: 618-630, 1943.

Discussion

DR. ROY W. MOHLER.—I think a report of this kind is very important because it constitutes the clinical findings where a large volume of obstetric work is done, and shows pretty clearly how seldom this complication arises in obstetrics. A few pertinent comments are in order.

It is instructive to know that 30 per cent of these patients delivered spontaneously, 25 per cent were delivered by forceps, 25 per cent by internal podalic version and extraction, and the remainder by cesarean section. In only five instances was the face presentation with recognized disproportion the indication for cesarean section. The results from the management of these cases were satisfactory when one reviews the tables critically.

Dr. Rudolph's presentation seems to indicate that face presentation of a fetus is a formidable complication in obstetric work; that no individual will encounter the complication frequently enough to acquire a familiarity which will enable him to manage the condition along any set plan. An effort should be made to recognize the condition fairly early. This can be accomplished by developing the habit of making more frequent and careful vaginal examinations in labor. These statistics have shown that one has ample time to observe what is happening with these patients in labor and that in the absence of frank disproportion, most of them will develop into chin anterior positions. After rotation has occurred, some will deliver spontaneously, others will need to be delivered with forceps. The presentations which remain chin posterior are the real problems, and it is in these few instances that some radical procedure must often be used. It is in these instances where good, sound obstetric experience and judgment must be exercised. For one, individual internal podalic version may be the procedure of choice; for another, individual cesarean section may be the procedure of choice. Whichever is the best and safest procedure for the individual to use, that is the procedure for him to choose.

DR. PHILIP F. WILLIAMS.—I would like to ask if attempts were made into any of these cases to convert a face into a vertex presentation to facilitate delivery?

DR. GEORGE PORRECCA.—I would like to know how often the diagnosis of face presentation was made prior to the patient going into labor?

DR. RUDOLPH (Closing).—There was one instance in which manual version was attempted when the cervix was approximately three fingers' dilated, but it was unsuccessful.

In one case the diagnosis of face presentation was made prior to delivery and cesarean section was resorted to.

RELATION OF MOTHERS' DIETS TO STATUS OF THEIR INFANTS AT BIRTH AND IN INFANCY

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THE effect of the mother's prenatal diet upon the status of her child at birth and its growth progress during the first year is still a controversial subject. McLester[1] states "... lack of protein in the mother's diet, unless extreme, will not affect the development of the fetus, for in case of need, the tissues of the mother are broken down to secure the amino acids necessary for construction of fetal tissues; it is only when starvation is extreme that the fetus suffers." Yet Burke, Harding, and Stuart[2] concluded from a study of 216 women and their offspring that "a significant relationship was found to exist between the protein content of the mother's diet during pregnancy and the birth length of her infant. This increase in length can be demonstrated with each additional increment of protein in the prenatal diet. . . . When the birth weights of the infants were considered in relation to the average number of grams of protein in the mothers' diet during pregnancy, it was found that an increase in birth weight could also be demonstrated with each additional increment of protein in the prenatal diet."

The efforts of various other workers suggests that material dietary deficiencies are capable of altering the structure and function of the developing fetus. Ebbs and Tisdall[3] have recorded a high correlation between the adequacy of the vitamin content of the mother's diet, the nature of delivery, and state of the infant at birth, and the infant's progress. Burke, Stuart, and associates[4] have reported an even higher relationship between the mother's diet and these factors, as well as the heights and weights of the newborn infants. Dieckmann's work[5] has further emphasized the importance of prenatal diet. Warkany[6] at Cincinnati has been able to produce certain skeletal defects in newborn rats by maintaining the rat mothers on grossly inadequate diets. There is as yet some question as to what elements of inadequacy are primarily responsible for these defects. Sontag and Munson,[7] working with rats, were able to show that drastic alterations in vitamin D and calcium intake were expressed in the chemical constitution of the offspring. Seegars[8] was able to show that the offspring of rats grossly deficient in protein intake during pregnancy produced newborn rats of distinctly smaller size and weight.

Despite the fact that there is evidence that certain deficiencies in the maternal diet will produce alterations in the structure and function of the developing fetus, it is not yet clear at what level of dietary deficiency such effects become apparent. Neither humans nor laboratory animals respond in increased growth rate in a direct arithmetical ratio to the amounts of food they ingest. They possess to some degree, rather, what might be called a nutritional homeostasis. That is, within limits, they utilize more efficiently or less well the food they ingest according to their growth and maintenance needs. A person of

low caloric intake will utilize very effectively every gram of carbohydrate he gets. On the other hand, in an individual who is fed so much sugar that the threshold of his kidneys is exceeded, some of the surplus will be discarded in the urine. Calcium and phosphorus are treated in a somewhat similar way. Added to this tempering influence is also the homeostatic action of the body in maintaining blood levels of numerous elements within relatively narrow ranges by utilizing body stores of protein, glycogen, calcium, phosphorus, etc., as well as food. Digesting four pounds of beefsteak a day for a couple of weeks by an adequately nourished individual will not raise substantially the level of blood proteins, and even amino acids in the blood are only temporarily increased, and to a limited extent. On the other hand, if no protein at all is ingested for a few days there is relatively little drop in blood proteins, and amino acids do not disappear from the blood stream. They are supplied rather from the protein tissues of the body which act as protein stores.

Such factors then act as buffers between the precipitous fluctuations of a mother's dietary intake and the continuous need of the fetus for body building and energy nutriments. Until we begin to test the abilities of such homeostatic mechanisms to maintain maternal blood levels of essential elements, it is not impossible that we may find it difficult to demonstrate conclusively relationships between maternal dietary intake to the size and condition of the infant at birth. It is entirely possible for extremes of maternal dietary deficiency in protein to express themselves in terms of small or inadequate offspring. Yet it does not necessarily follow that the mother whose daily protein intake is 75 Gm. will produce an infant inferior in size or quality to the woman whose intake is 85 Gm. per day. It may be true even that if the dietary intake is 65 Gm., no deficiency of the infant can be demonstrated; or perhaps 55 Gm. might be the limit. It is also probable that there are individual differences in this respect—differences perhaps dependent upon the various metabolic functions of the mother as well as the adequacy of maternal stores of various food elements at the beginning of pregnancy. It may very well make an appreciable difference to the fetus whether his mother is a six foot woman weighing two hundred pounds attempting to support herself and him on a daily intake of 65 Gm. of protein, or whether she weighs a hundred pounds and ingests the same amount of protein. If so, it would be difficult to assume that an infant will necessarily be defective or in poor condition at birth if the mother's protein diet is 53 Gm. per day instead of 60. Perhaps all these factors, plus individual differences in absorption from the alimentary tract, would prevent our finding a very high correlation between *ingestion* and the size of the newborn infant, providing we are dealing with a group whose nutritional level is not gravely deficient. No such marked effect upon size of infant at birth could be expected in our group as that shown by Smith[9] and by Antonov.[10] Both of these investigators studied the effects of partial starvation of populations at certain periods of the war, and were able to show conclusively that maternal diet affected size of the newborn.

For the past ten years a part of the study of the Fels Research Institute has included the close observation of pregnant women during the last six or seven

months of gestation and the subsequent careful study of their offspring. One factor studied has been the diets of these women. The quantity of data we have now accumulated seems to us to justify analysis in an attempt to determine whether from it relationships between prenatal nutrition, the status of the infant at birth, and its subsequent growth progress can be demonstrated. This paper will present one portion of such an analysis, namely, a comparison between the mothers' average daily protein intake and the birth weights, birth lengths, and growth progress of their infants. Rate of appearance of ossification centers in relation to mothers' protein intake will also be considered.

Material

The 205 mothers and their infants considered in this study have been under observation at the Institute for an extended period of time. These subjects volunteered their cooperation not because it was solicited, but because they were genuinely interested in participating in the study. As a group, they might be described as belonging to the upper middle class. They are white women of well-blended American stock and are residents of Ohio. They cover a considerable income range, particularly since some of the observations were made during the 1931 to 1934 period. The majority of them have not been so pressed financially as to be unable to afford nutritious food, but many had poor dietary habits. Most of these mothers were under observation during the last six or seven calendar months of pregnancy and were seen at least once a month. During the last part of this period they were examined once a week or oftener. Laboratory data such as basal metabolism rates, hemoglobin, red cell counts, and hematocrit readings were collected at regular intervals during pregnancy. A later study will present such data and its relationship to nutritional intake.

Dietary records were obtained in the following manner. Each pregnant woman was asked to record daily the exact foods she had consumed and as nearly as possible the exact amounts. She was urged not to rely on her memory as to what she had eaten the day previously. In general, dependence upon memory even for one day in the recording of diets must be considered fallacious. There are few persons who can give an accurate account of all the foods eaten, together with a description of their quantities twenty-four hours later. Each mother was made to feel that if she occasionally missed a day's record because of unusual circumstances such as company or a holiday away from home, no one would be concerned about it. Most of these records were kept for a period of sixteen weeks or longer, a considerable number of them for six or seven months. Each week's record consisted of seven consecutive days so as to eliminate a preponderance of unusual days as Sundays or washdays. Once a month the nutritional histories were brought in and checked with the patient by a nutritionist in order to be sure that no misunderstanding existed and that the records were reliably kept and were representative.

At no time was any mother instructed as to what she should eat. Not one of these mothers could therefore have any sense of guilt because she had not adhered to a diet we had suggested as being necessary for the adequate protection of her growing infant. This point is extremely important in acquiring dietary records, because few patients care to brave the displeasure of a diet-conscious physician for a small item as a bottle of milk. Most of them feel it is much easier to report what is expected.

From this battery of nutrition records quantitative analyses were made in terms of average daily intake of protein, calories, minerals, and the various vitamins. A full description of our method of data collection and analysis is

given in another paper.[11] Quantitative values for average daily intakes of protein in grams are the basis for this present study.

Anthropometric measurements including crown-heel length are taken on the newborn infants at home or at the hospital by members of the Fels staff, usually within twenty-four hours of birth. A physical examination is made by the Fels pediatrician at this time. Whenever possible complete skeletal x-rays are taken by the hospital staff for us. Subsequently, infants are brought to Fels at one, six, and twelve months for physical examination, anthropometric measurements, and x-rays. Measurements of the children used in this study are: weight in kilograms, crown-heel length in centimeters, and number of ossification centers present.[12] The illness histories, physical examinations, and infant nutrition records obtained during these visits will be considered in a later paper.

All cases of hyperthyroidism, toxemias of pregnancy, multiple births, erythroblastosis fetalis, and other interfering illnesses were omitted from this study. Tables show birth weights, lengths, etc., of the group when prematures are excluded, and also when they are included in the group. Prematurity as used in this study is defined as a child of less than eight months menstrual age.

The mothers' weights used are the weights at the last menstrual period prior to pregnancy.

Method

The mothers were divided into five groups according to their average daily intake of protein: 85 Gm. or more, 70 to 85 Gm., 55 to 70 Gm., 45 to 55 Gm., and under 45 Gm. per day. These particular groupings were chosen to correspond to those used by Burke and associates, so that results of the two studies may be easily compared.

Mean birth weights and birth lengths of the infants were calculated for each protein group. Significance of the difference between the means for the highest (over 85 Gm. per day) and lowest (under 55 Gm. per day) protein groups was tested. This same procedure was applied to weight and length at one, six, and twelve months of age. The number of ossification centers for each protein group at each age was similarly studied.

Pearson coefficients of correlation (r) between the mothers' prenatal protein intake and the weight, length, and ossification of the infants were calculated for each age. All correlations were computed both excluding and including premature infants. Significance of each correlation was tested.

Growth patterns could not be adequately studied using the entire group of infants, since there are a number of incomplete cases in each protein group. An extreme case with data missing at one or more age levels would distort the growth curve. To adequately study growth changes with age, a longitudinal study was made using the thirty highest and thirty lowest cases (half male, half female) with *complete* data on length and weight. Significance of the differences between the means of the highest and lowest cases was tested, as were the differences in status for each group between birth and twelve months. It should be remembered that the reliability of growth curves is greatly increased by the use of longitudinal data.

The use of T-scores makes it possible to combine the sexes, quite as Burke and his co-workers combined them by using percentiles. A T-score is derived by adding 50 to ten times the standard deviation (sigma deviation) from the mean for any given characteristic.

Results

The means (m) and sigmas (σ) of weight, length, and ossification for each protein group are presented in Tables I, II, and III. The coefficients of correlation (r), together with their significance, are given directly below each age

group. Significance of the difference between the highest (over 85 Gm. per day) and lowest (under 55 Gm. per day) protein groups is indicated only where significant at the 0.05 level of probability or better; other differences have been tested, but are not significant by this criteria. Longitudinal growth curves of weight and length for the sixty most extreme complete cases are shown in Fig. 1. All weights, lengths, and numbers of ossification centers are expressed as T-scores.

Weight (see Table I).—At birth and one month, excluding premature infants, there are no progressive decreases in mean weights with decreasing protein intake as would be expected if a high degree of association existed between these factors. When premature infants are included, there is a suggestive relationship at both birth and one month. Examination of our data revealed that this greater association is due to the addition of a single very extreme case, protein = 26 Gm. per day, weight = $-2.2\ \sigma$ at birth and $-2.9\ \sigma$ at one month. (This case is not included at six or twelve months.) None of the correlations are significant at these two ages, nor is there a significant difference between the means for the highest and lowest protein groups.

TABLE I. WEIGHT (T-SCORES; MALE AND FEMALE)

		Excluding Premature			Including Premature		
Birth:	Protein, Gm./Day	N	M	± σ	N	M	± σ
	85 or more	19	54	10	20	53	12
	70 to 84	81	51	7	83	50	8
	55 to 69	74	51	10	76	51	10
	45 to 54	19	52	7	19	52	7
	under 45	3	56	-	5	49	9
	under 55	22	52	7	24	51	8
	Correlation:	r = +0.04 (N = 196) (not significant)			r = +0.06 (N = 203) (not significant)		
One Month:	Protein, Gm./Day	Excluding Premature			Including Premature		
		N	M	± σ	N	M	± σ
	85 or more	16	54	10	16	54	10
	70 to 84	70	51	8	71	50	9
	55 to 69	66	49	9	67	49	9
	45 to 54	16	52	6	16	52	6
	under 45	3	57	-	5	45	17
	under 55	19	52	7	21	50	10
	Correlation:	r = +0.06 (N = 171) (not significant)			r = +0.16 (N = 175) (not significant)		
Six Months:	Protein, Gm./Day	Excluding Premature			Including Premature		
		N	M	± σ	N	M	± σ
	85 or more	17	54	10	17	54	10
	70 to 84	68	51	10	70	51	10
	55 to 69	66	51	9	68	51	9
	45 to 54	17	51	9	17	51	9
	under 45	3	51	-	4	48	-
	under 55	20	51	9	21	50	9
	Correlation:	r = +0.10 (N = 171) (not significant)			r = +0.12 (N = 176) (not significant)		
Twelve Months:	Protein, Gm./Day	Excluding Premature			Including Premature		
		N	M	± σ	N	M	± σ
	85 or more	17	54*	9	17	54*	9
	70 to 84	67	51	11	69	51	12
	55 to 69	65	49	10	67	50	10
	45 to 54	17	48	11	17	48	11
	under 45	2	42	-	3	41	-
	under 55	19	47*	11	20	47*	11
	Correlation:	r = + 0.21 (N = 168) P = 0.05			r = +0.22 (N = 173) P = 0.05		

*Difference between highest (85 or more) and lowest (under 55) protein groups is significant at the 0.05 level of probability.

At six months there is again a suggestive slight decrease in mean weights with decreasing protein. The differences between the highest and lowest groups are not significant, nor are the correlations.

A significant association between protein intake and weight of the infant is shown only at twelve months. There is a definite, progressive decrease in mean weights with decreasing protein, and a difference significant at the 0.05 level of probability between the extreme protein groups. The coefficients of correlation are also significant at the 0.05 level of probability.

Length (see Table II).—Length shows a very similar pattern of association with prenatal protein intake to that shown by weight. At birth and one month there is little apparent association until the premature infants are included. Here, as with the weights, the addition of the same extreme case (protein = 26 grams; length = $-3.5\ \sigma$ at birth, $-4.0\ \sigma$ at one month) creates a slight progressive decrease in mean length with decreasing protein intake. The differences between the highest and lowest groups are not statistically significant, nor are the correlation coefficients.

There is no significant association shown with length at six months.

TABLE II. LENGTH (T-SCORES; MALE AND FEMALE)

		Excluding Premature			Including Premature		
Birth:	Protein, Gm./Day	N	M	± σ	N	M	± σ
	85 or more	11	55	13	12	54	13
	70 to 84	44	52	7	44	52	7
	55 to 69	52	50	8	53	50	8
	45 to 54	14	50	9	14	50	9
	under 45	2	55	-	4	42	-
	under 55	16	51	9	18	49	12
	Correlation:	r = +0.13 (N = 123) (not significant			r = +0.17 (N = 127) (not significant)		
One Month:	Protein, Gm./Day	Excluding Premature			Including Premature		
		N	M	± σ	N	M	± σ
	85 or more	14	54	10	14	54	10
	70 to 84	61	52	10	62	52	10
	55 to 69	59	49	11	60	49	11
	45 to 54	16	51	10	16	51	10
	under 45	3	60	-	5	46	20
	under 55	19	52	10	21	50	14
	Correlation:	r = +0.09 (N = 153) (not significant)			r = +0.16 (N = 157) (not significant)		
Six Months:	Protein, Gm./Day	Excluding Premature			Including Premature		
		N	M	± σ	N	M	± σ
	85 or more	16	52	7	16	52	7
	70 to 84	68	50	9	70	50	10
	55 to 69	62	48	9	64	47	10
	45 to 54	17	48	10	17	48	10
	under 45	3	55	-	4	53	-
	under 55	20	49	9	21	49	9
	Correlation:	r = +0.12 (N = 166) (not significant)			r = +0.11 (N = 171) (not significant)		
Twelve Months:	Protein, Gm./Day	Excluding Premature			Including Premature		
		N	M	± σ	N	M	± σ
	85 or more	16	53*	8	16	53*	8
	70 to 84	64	51	10	66	51	11
	55 to 69	64	48	10	66	48	10
	45 to 54	16	47	9	16	47	9
	under 45	2	47	-	3	48	-
	under 55	18	47*	9	19	47*	9
	Correlation:	r = +0.22 (N = 162) P = 0.05			r = +0.17 (N = 167) (not significant)		

*Difference between the highest (85 or more) and lowest (under 55) protein groups is significant at the 0.05 level of probability.

As with weight, the greatest degree of relationship between the prenatal protein intake and the length of the infants is present at twelve months. There is a definite, progressive decrease in means with decreasing protein, both excluding and including premature infants, with a significant (P = 0.05) difference between the lengths of the protein groups over 85 Gm. per day and under 55 Gm. per day. Both correlations at twelve months are significant at the 0.05 level of probability.

Ossification (see Table III).—At birth there is a suggestive, though not statistically significant, *inverse* association between the protein intake of the mother and the number of ossification centers present. With each decrease in protein there is an increase in the number of centers present. The differences between the extreme groups are not significant, nor are the correlations.

TABLE III. OSSIFICATION (T-SCORES; MALE AND FEMALE)

		Excluding Premature			Including Premature		
Birth:	Protein, Gm./Day	N	M	± σ	N	M	± σ
	85 or more	7	47	8	7	47	8
	70 to 84	22	50	10	22	50	10
	55 to 69	31	51	7	32	51	7
	45 to 54	11	53	14	11	53	14
	under 45	1	63	-	2	58	-
	under 55	12	54	13	13	54	13
	Correlation:	r = -0.21 (N = 72) (not significant)			r = -0.20 (N = 74) (not significant)		
One Month:	Protein, Gm./Day	Excluding Premature			Including Premature		
		N	M	± σ	N	M	± σ
	85 or more	14	54	13	14	54	13
	70 to 84	57	49	9	58	49	9
	55 to 69	59	49	10	60	49	10
	45 to 54	16	52	13	16	52	13
	under 45	3	60	-	4	59	-
	under 55	19	53	13	20	53	13
	Correlation:	r = -0.05 (N = 149) (not significant)			r = -0.06 (N = 152) (not significant)		
Six Months:	Protein, Gm./Day	Excluding Premature			Including Premature		
		N	M	± σ	N	M	± σ
	85 or more	15	55	11	15	55	11
	70 to 84	64	50	7	66	50	7
	55 to 69	59	50	6	61	49	6
	45 to 54	16	54	12	16	54	12
	under 45	3	61	-	4	59	-
	under 55	19	52	12	20	55	12
	Correlation:	r = -0.04 (N = 157) (not significant)			r = -0.04 (N = 162) (not significant)		
Twelve Months:	Protein, Gm./Day	Excluding Premature			Including Premature		
		N	M	± σ	N	M	± σ
	85 or more	15	56	10	15	56	10
	70 to 84	62	49	9	64	49	9
	55 to 69	59	48	7	61	48	7
	45 to 54	16	52	16	16	52	16
	under 45	2	55	-	3	54	-
	under 55	18	53	15	19	53	15
	Correlation:	r = +0.03 (N = 154) (not significant)			r = +0.03 (N = 159) (not significant)		

No significant relationship is shown at one, six, or twelve months. There is, however, a peculiar, consistent pattern shown at each of these ages. The greatest number of centers is present in the extreme protein groups, those over 85 and those under 55 Gm. per day. The in-between groups (between 55 and 85) show the fewest number of centers at all three age levels. Certainly differences in maternal protein intake are not manifested in retarded skeletal growth of the infants in this group.

Growth Curves (see Fig. 1).—The sixty most extreme cases with complete data at all ages were used for a longitudinal study of the differences and growth changes. The difference between the thirty highest and thirty lowest cases is 29 Gm. of protein, significant at greater than the 0.001 level of probability. In spite of the extreme differences between the groups chosen for comparison, the differences shown in weight and length are not statistically significant or even nearly so (the greatest difference has a probability of 0.4). Except for birth weight where there is no difference, infants in the lowest protein group are somewhat shorter and lighter at all ages. There is a greater difference in lengths than in weights of the two groups. There is no observable age trend for either length or weight, nor any significant difference between various age levels.

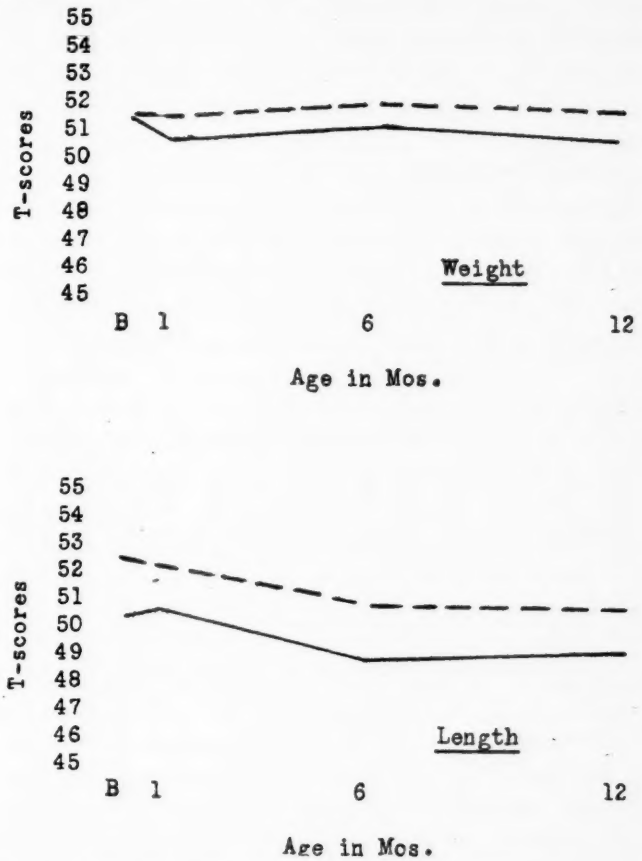

Fig. 1.—Mean growth patterns for 30 highest and 30 lowest complete cases.

— — — — — = Highest protein group, N = 30; mean protein = 58 (T-score).
———————— = Lowest protein group, N = 30; mean protein = 38 (T-score).
(No significant difference between high and low groups; no significant age change.)

One might advance the hypothesis that large women, other factors being equal, eat much protein and that large women also have large babies. If so, a false implication of the importance of high protein consumption might emerge. However, the correlation between mother's weight and her calculated protein ingestion is –0.04. Since there is no apparent relationship between mother's size and her protein ingestion, no spurious effect can be operative in our group.

Discussion

Weight.—While correlation coefficients between infant weight and maternal protein intake values are on the positive side at each age level, it is only at twelve months that these coefficients become statistically significant. The fact that the three coefficients, none of which is statistically significant, are all on the positive side is mildly suggestive of a positive though slight relationship.

Length.—Only one of the correlation coefficients between infant's length and mother's protein intake values is at a significant level, and that barely so. Again, however, all of the coefficients are positive, a fact which suggests the possibility of some relationship between mother's protein values and length.

Ossification.—There are no statistically significant correlation coefficients between the ossification of the infants during the first year of life and the mother's protein intake. Some of the coefficients are positive and some negative, but all are small.

The rather considerable difference in the results of our study as compared with that of Burke and Stuart is, at first sight, somewhat puzzling. Burke found a correlation coefficient of 0.80 between protein intake and length of the child. She also found a higher relationship between protein intake and the infant's weight. Yet, in our series of cases, approximately the same number of mothers and children were studied, but the relationships we have found are on the borderline of significance and far below those of Burke and associates. There are, perhaps, a number of differences in the study which may account for our differences in result. It is difficult from Burke's description to understand exactly the method she used to arrive at numerical values for the protein intake for the women she studied. In an early publication Burke states "a closer analysis of data obtained by the nutrition history method is unwarranted. and more exact calculation of diets is justified only in the case of weighed samples."[4] She also states that "the average daily protein content of the diets has been estimated in grams. Table I shows the standards used in rating the protein intake of the mothers."[2] It is not clear to us whether she assigned a rating of excellent, good, fair, and poor to the various diets, and then on the basis of nutrition standards stated by others assigned a numerical value to the ratings, or whether she estimated directly from her nutrition histories the grams of protein ingested. She apparently did not arrive at her values by a method of calculation of values from food tables—the method we have used. This difference in technique may account for some of the differences in results.

In the Burke studies the calculated daily intake of protein tended to be lower than in our series. For example, 61 of 183 mothers had protein intakes of 54 Gm. per day or under, whereas, in our series, only 24 mothers of a group of 203 have protein diets under 55 grams. Thus, the drain on protein reserves by Burke's mothers probably was greater than in our series, and the effects of inadequate protein diet might be supposed to be greater.

Burke has apparently included in her series several cases of toxemia of pregnancy which were treated, at least in some instances, by being placed upon a very low protein diet. It is well known that infants of toxic mothers tend

to be very small, not because of low protein intake primarily, but apparently as a result of thromobsis of the placental vessels. The effect of including even a few such infants in the series would be to increase tremendously the correlation between mother's protein intake and size of the infant. Yet, actually, in those instances both protein intake and size of the infant would be dependent upon a third factor—the toxemia.

Summary

In a study of 203 mothers' diet histories and the relationship to the length, weight, and ossification of their infants at birth, one month, six months, and twelve months of age, we have been unable to demonstrate unequivocably a relationship between any of these factors and protein intake of the mothers during pregnancy. There is a suggestion of a relationship between weight and length and protein intake. Our conclusion from this study is not that protein intake has no effect upon the status of the infant at birth or during the first year, but rather that protein intake must fall below the levels current in our groups before such an effect is clearly demonstrable. Our results should not be interpreted as a basis for disregarding the importance to the child of good nutrition during pregnancy.

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A PREMATURE SURVIVAL INDEX AND THE CONDUCT OF PREMATURE LABOR

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THERE is today no unanimity as to precisely what constitutes a "premature infant." No standard has been universally accepted. The frequent statistical division of prematures into viable and nonviable, appears to us to be unsound, illogical, and contrary to basic definitions. In the first place, the term "viable premature" is a double positive, for a premature infant, by definition, is one which is viable. It follows then that so-called "nonviable prematures" are, in the strict sense, abortions. We are of the opinion that, for statistical purposes at least, the term *premature* should be reserved for fetuses born at varying periods before they can be expected to survive with the ease shown by those carried nearer to term, and *abortion* for those born before the twenty-eighth week of gestation. Furthermore, the terms premature infant and viable infant are commonly used synonymously. It is acknowledged that many small premature infants, even when delivered alive in good condition, will not survive. Moreover, occasionally a fetus, which, according to all current standards, is an abortion, will survive under appropriate pediatric care. An excellent example of the latter is the fetus reported by Monro[1] to have had a minimum recorded weight of 420 Gm. (0.924 pounds). This, incidentally, is the smallest surviving infant on record.

Various criteria are in use to determine whether a fetus is viable. Thus, on the basis of duration of pregnancy, a fetus which has remained in utero twenty-eight weeks is generally said to be a premature.[2] The lower limit of prematurity recognized by DeLee[3] is twenty-six weeks' gestation. The Catholic church,[4] too, recognizes a fetus from a twenty-six weeks' gestation as being premature. For obvious reasons, duration of pregnancy in some instances as calculated from onset of the last menstrual period is inaccurate. It must be recalled that many women do not record the dates of their menses and therefore have no precise data on the last menstrual period. Again, the date of ovulation and of conception cannot be dated with precision from the onset of the previous menstrual cycle, but rather from the onset of the next menses, which, of course, does not occur in the event of pregnancy. The inaccuracy from menstrual history becomes even greater in those few women who do not menstruate regularly, and in those few with cycles far above twenty-eight days. Notwithstanding these inherent errors, which careful history taking will constantly reduce, and in view of the fact that the great majority of patients do menstruate roughly every twenty-eight days, the gestational period as calculated from onset of last menses is still a usable factor.

Another standard for prematurity, and the one most commonly used, is birth weight or minimum recorded weight, since many premature infants are not weighed at birth, but this function postponed for days, until such time as the premature infant is considered to be in good enough physical condition to be handled or until it expires. The generally accepted weight limits for prematurity are 1,500 Gm. (3.3 pounds) and 2,499 Gm. (5.5 pounds). The lower limit is of particular concern to us. There are a fair number of fetuses of gestations of at least twenty-eight weeks with birth weights below 1,500 Gm., even some below 1,000 Gm. (2 pounds 3 ounces). This occurrence is frequent enough to have prompted Haas[5] to suggest 1,000 Gm. as the lower weight limit of prematurity. Naturally, those premature infants with birth weights below 1,000 Gm. have a very poor expectancy for life, yet it is interesting to record that a recent survey of the literature[5] reveals that there are at least 54 such cases on record. Comment on the smallest of these has already been made. With the above facts in mind, it becomes quite obvious that birth weight is indeed a very poor criterion of prematurity. We must remember that birth weight of the newborn is an index of the weight of its ancestors, and, since there are very wide ranges in weights of adults, there will, accordingly, be great normal variations in weights of newborn infants, whether they are born prematurely or at or near term. Again, some maternal diseases, notably chronic nephritis, have a very detrimental effect upon fetal nourishment, and frequently cause children to be produced far below the birth weight normally expected for the period of gestation. The ease in rearing these, if born alive in good condition, corresponds to the advanced gestational period and not to the subnormal birth weight. In other words, they do not afford the difficulty found with premature infants of the same weight born of non-nephritic mothers. Three of the above noted 54 raised premature infants with weights of less than 1,000 Gm. were reported by Haas,[5] and it is an interesting commentary that two of these three were born of nephritic mothers. Occasionally one finds very marked differences in birth weight of a pair of identical twins. An outstanding example of this was noted by one of us (A. L. D.) when single-ovum twins were delivered at thirty-three weeks' gestation with one weighing 1,005 Gm. and the other 2,260 Gm. The smaller was raised with very little more difficulty than the larger.

Still another standard for determination of prematurity is body length. Crown-heel length or standing height is commonly used. The generally accepted limits of this criterion for prematurity in most teaching institutions are at least 35 cm., but less than 45 cm. total length. When we realize that body length is an hereditary factor, it is immediately apparent that this standard is reliable only in children born of parents of average height. Anyone who has measured the length of many newborns, and especially he who has remeasured some by the same or by various methods, will recognize certain inherent difficulties with the precise determination of this diameter of a newborn. The commonest method of mensuration here is to suspend the newborn from the ankles while measuring along the side of the body with a tape. A washable tape is, of course, not precise. The newborn with decreased muscle tone, as is

typical with premature infants, will measure long, due to undue lengthening at all joints, whereas the vigorous, well-muscled term or postmature newborn will not always relax immediately upon being picked up by the ankles and will thus produce a short measurement. The highest precision can be obtained with an anthropometer after some experience—experience primarily on the part of the assistant who stretches the newborn out at a maximum length on his back on a non- or poorly padded examining table.

The most unreliable standard of viability or prematurity is that attempt by law governing reportable gestations. The Model Vital Statistics Act of 1941 requires that all gestations advanced to the fifth month be reported. Since there is no specification to the contrary, it is assumed that calendar months are meant. Sixteen states and the District of Columbia have other legal limits, varying from Maryland (any recognizable product of conception) to those of the states of Washington and Indiana (seven months or over).

Not infrequently more than one standard is utilized in order to ascertain the presence of prematurity. For example, Dana[6] defines the premature infant as one whose birth weight is between 1,500 and 2,499 Gm., or whose total length is between 35 and 44.9 cm., regardless of the duration of pregnancy. This combination is fairly commonly employed in teaching institutions. We are aware of none utilizing a combination of more than two, although Hess and Chamberlain[7] contend that age, length, and weight of the premature infant are the main factors concerned with its viability.

From the foregoing, it appears quite obvious that there are several criteria in use for the diagnosis of prematurity, but that all are variable factors. It has occurred to one of us (H. W. J.) that a combination of a larger number of factors of the small premature infant should produce less inaccuracy in the diagnosis of prematurity and in prognosticating the probable outcome than has thus far been possible with any of these factors used alone. The assumption is that the inaccuracies in single factors will tend to be equalized when combined with each other. Accordingly, we have developed an index for prematurity from a combination of five factors.

Only twenty-three premature infants thus far comprise the series. They are nonselected, but consecutive private cases delivered at St. Joseph's Maternity Hospital over a period of ten months. Stillbirths and those succumbing in the immediate antenatal period are not included.

The factors used to establish the five-point premature survival index are the following: (a) gestational period is calculated from the first day of the last normal menstrual period regardless of regularity or irregularity of the menstrual cycle in each instance. In the current series the cycles varied from twenty-eight to thirty-two days with one exception, in which the cycle was forty-five to sixty days, and nothing is known of the cycles of three other patients. (b) Weight of the newborn was obtained in ounces. (c) The total, or crown-heel, length was obtained in inches in the usual manner, i.e., by measuring with a steel tape along the side of the body suspended at the ankles. (d) Occipitofrontal circumference was recorded in inches. (e) The circumference

of the chest was obtained at the level of the xiphisternal joint and recorded in inches. Some few infants were weighed immediately after delivery, but all were measured and weighed within twelve hours of birth. Each newborn infant was promptly placed in a preheated incubator in the delivery room, transported to the premature nursery in this incubator, in which it remained under the competent supervision of the pediatric staff. We are not presenting the details of premature infant care supplied this group of newborn infants. Suffice it to say that the premature nursery at St. Joseph's Maternity Hospital is staffed by a group of pediatricians and nurses who have reduced the uncorrected premature infant mortality rate from 45 per cent to 22 per cent since instituting the present regime in an isolated unit of the hospital. Tyson[8] reports similar reduction in this rate at the Philadelphia Lying-In Hospital with a rate of 56 per cent in 1931 and 26 per cent in 1941.

The index was obtained by adding gestation in weeks, weight in ounces, crown-heel length in inches, head circumference in inches, and chest circumference in inches, and then dividing the total by five. This resulted in indexes ranging from 19.2 to 25.7 for the twenty-three infants. The important data for each is recorded in Table I. Length of labor is not included in the table, but is of considerable importance in as much as precipitate labor is definitely detrimental to any fetus and may be the specific cause of stillborn or neonatal death in premature labors. In this series, there were five precipitate labors, i.e., total labors lasting three hours or less (Cases 3, 6, 8, 16, and 20). The longest total labor was seventeen hours (Case 13). Excluding the three cesarean sections, all of which were done electively, the average labor lasted 7.2 hours. The three mothers delivered by cesarean section were given as anesthetic agents: spinal novocain, local novocain, and cyclopropane, respectively. The remaining twenty which were delivered vaginally received: no anesthesia (four), pudendal block (two), cyclopropane (nine), cyclopropane and ether (one), ether (two), and cyclopropane with nitrous oxide (two). The analgesic drugs used in these labors are too numerous to record. It is, however, worthy of mention that ten received no analgesia in labor, and eight more who received none within three hours of delivery. Two women in premature labor received demeral (100 mg.) and hyosine ($\frac{1}{150}$ grain) hypodermically within one hour of delivery. Another was given pantopon ($\frac{1}{3}$ grain) hypodermically twenty minutes before delivery, and the remaining two received nembutal ($1\frac{1}{2}$ grains) orally one and two hours, respectively, before delivery.

Eleven of these twenty-three premature labors were cared for by physicians in general practice, two by nonboard specialists in obstetrics, and the remaining ten by diplomates of the American Board of Obstetrics and Gynecology, three cases being the largest number cared for by any one physician. Fifteen of the mothers were multiparas, one having had eight previous term pregnancies. The past obstetric history on one is not known, and two were essential primiparas, i.e., had had one or more previous abortions. The remaining five were primigravidas, one of these an elderly primipara. The age range of the mothers coincided with the usual variations on an obstetric service, the youngest being 19 years of age and oldest 41 years, both primigravidas.

TABLE I. DATA ON 23 PREMATURES FOR PREMATURE SURVIVAL INDEX

CASE NO.	WEEKS GESTATION	WEIGHT (OUNCES)	CROWN-HEEL LENGTH (INCHES)	HEAD (INCHES)	CHEST (INCHES)	INDEX	TYPE OF DELIVERY	TIME LIVED	AUTOPSY
1*	32½	40	15	10	9	21.3	Cesarean section	2 days	None
2	32½	57	15.6	11.8	10.2	25.6	High forceps	Living	----
3	28½	35.5	14.4	10	8.4	19.4	Breech extraction	Living	----
4	29½	51	16	10.5	9.5	23.3	Spontaneous	Living	----
5	29½	60.5	16.5	11.5	10.5	25.7	Spontaneous Episiotomy	Living	----
6	28	36	15	10.2	11	20.4	Low forceps Episiotomy	Living	----
7*	28⅓	39	16.2	10.2	8.75	20.5	Spontaneous	6 hours	None
8	29½	43	16	10.5	9.5	21.7	Spontaneous	Living	----
9	29⅔	49	15.5	11	10.5	23.1	Spontaneous	Living	----
10	28	41	15	10.5	9	20.7	Spontaneous	11 hours	None
11	27	35.5	14.8	10	8.75	19.2	Spontaneous	39 hours	None
12*	30½	43	15.5	10.2	9.5	21.7	Spontaneous	6 days	None
13	30½	48	17	11	9.75	23.3	Breech extraction Episiotomy	Living	----
14	28	42	15.5	10.5	9.2	21.0	Spontaneous	Living	----
15	28½	36	15.25	10	9	19.8	Low forceps Episiotomy	Living	----
16	32⅓	52.5	16.5	11.5	10.2	24.6	Spontaneous Episiotomy	Living	----
17*	29½	36	15	10.75	8	19.9	Cesarean section	20 hours	None
18*	31⅓	40	15.25	10.8	8.7	21.2	Breech extraction	25 hours	Atelectasis
19*	30½	55	16.5	11.5	9	24.5	Spontaneous Episiotomy	16 hours	Torn falx and tentorium
20	32½	38	14.25	10	9	20.7	Spontaneous	Living	----
21	32	39	16.25	10.75	9	21.4	Cesarean section	Living	----
22	28	41	15.25	10.25	9.5	20.8	Spontaneous	4½ hours	None
23	27	40	16.25	10.5	8.5	20.5	Breech extraction	4 hours	Prematurity

*Not included in final analysis—see text.

Eight of these twenty-three pregnancies and labors had no known complications. In nine of the remaining fifteen there was premature spontaneous rupture of the membranes. There were only three toxemias of pregnancy, namely, two with severe pre-eclampsia, and the other with pre-eclampsia superadded to arteriosclerosis. Still another presented pyelo-nephritis which she had had in her only other pregnancy and one had a moderately severe hypochromic microcytic anemia, while the twenty-third delivered a badly macerated twin.

For purposes of arriving at a premature survival index, six of the above cases are eliminated from the final analysis since, for various reasons given herewith, the corresponding premature infants were not or are assumed not to have been delivered in good condition.

CASE 1.—A 31½ weeks' gestation delivered by cesarean section under spinal novocain anesthesia at another hospital and transported by automobile to the St. Joseph's Maternity premature nursery.

CASE 7.—A 28⅓ weeks' gestation from a multigravida (three previous abortions) who had obvious premature separation of the normally implanted placenta. There was no autopsy, but the clinical impression of the cause of neonatal death after six hours was cerebral edema and bilateral atelectasis.

CASE 12.—A 30½ weeks' gestation delivered spontaneously in bed one hour after a hypodermic of demeral and hyosine, and which had partial amputation (?) of two fingers allowing the speculation, in the absence of an autopsy, of the presence of internal anomalies.

CASE 17.—A 29½ weeks' gestation in a primigravida with a long history of infertility and with a diagnosis of severe pre-eclampsia superadded to hypertensive vascular disease, delivered by cesarean section after weeks of palliation. Autopsy revealed only prematurity.

CASE 18.—A 31⅓ weeks' gestation in a multipara with an apparently normal pregnancy, but delivered by breech extraction under cyclopropane and ether anesthesia. Autopsy showed atelectasis and periportal infiltration.

CASE 19.—A 30½ weeks' gestation in a secundipara whose pregnancy is said to have been normal, and who was delivered spontaneously with episiotomy under cyclopropane anesthesia one hour after demeral-hyosine analgesia. Atelectasis, torn falx cerebri, and tentorium cerebelli, as well as adrenal hemorrhage, were discovered at postmortem examination of this premature.

In Table II, the seventeen premature infants included in the final analysis are listed in ascending order of value of the premature survival index. Three factors of this index, namely, gestational weeks, birth weight, and crown-heel length, are included along with survival of each infant. Obviously, the series is too small to allow deduction of permanent conclusions. However, some few suggestions are worthy of comment. For example, all premature infants with an index of at least 21.0 were raised, whereas only 50 per cent of those with a smaller index survived. The upper bracket includes gestations which are presumed to have been carried for 28 to 33½ weeks, and premature infants with birth weights ranging from 39 ounces (2.4 pounds) to 60.5 ounces (3.8 pounds). Of particular interest in this table is the absence of correlation between gestational period, birth weight, and total length of the infants. An outstanding example of this is seen in Case 5 where the gestational period is said to have been only 29½ weeks, whereas the infant was the heaviest and the longest in the series, these latter two factors helping to produce the largest index. In this connection, it should be pointed out that the mother menstruated regularly every twenty-eight days, and that she first perceived fetal movements at a time which would tend to confirm the accuracy of her menstrual history. In the lower index bracket is found Case 20 which presented the shortest and one of the lighest infants which is believed to have been one of the longest retained in utero in this series.

It is these apparent inconsistencies in one or more of the commonly employed criteria of prematurity which we believe will be overcome by the use of a sizeable number of factors such as offered by our five-point premature survival index. We believe that after further experience we will be able to say that every premature infant born alive in good condition with an index of at least twenty-one should be reared. Very probably experience will show that this figure should be smaller. We hasten to say that we do not consider premature infants below any arbitrarily chosen figure for one or more factors as hopeless cases. No matter how small the liveborn product of conception, it is given

TABLE II. PREMATURES LISTED IN ASCENDING ORDER OF VALUE OF PREMATURE SURVIVAL INDEX. THREE FACTORS OF INDEX INCLUDED

CASE NO.	INDEX	GESTATION (WEEKS)	WEIGHT (OUNCES)	CROWN-HEEL LENGTH (INCHES)	TIME SURVIVED
11	19.2	27	35.5	14.8	39 hours
3	19.4	28½	35.5	14.4	Living
15	19.8	28½	36.0	15.25	Living
6	20.4	28	36.0	15.0	Living
23	20.5	27	40.0	16.25	4 hours
10	20.7	28	41.0	15.0	11 hours
20	20.7	32½	38.0	14.25	Living
22	20.8	28	41.0	15.25	4½ hours
14	21.0	28	42.0	15.5	Living
21	21.4	32	39.0	16.25	Living
8	21.7	29½	43.0	16.0	Living
9	23.1	29⅔	49.0	15.5	Living
4	23.3	29½	51.0	16.0	Living
13	23.3	30½	48.0	17.0	Living
16	24.6	32⅓	52.5	16.5	Living
2	25.6	33½	57.0	15.6	Living
5	25.7	29½	60.5	16.5	Living

every opportunity to live that expert pediatric care can afford. As seen in Table II, some of the smallest infants can be reared, and it seems impossible to predict from weight exactly which ones will survive.

Our aim is to continue with this problem until we obtain a large series from which positive conclusions can be drawn. We should be able eventually to say that every premature infant above a certain level should be reared. Furthermore, it should be possible to determine probable survival rates for each group below this level. Such predictions should be possible in the absence of congenital anomalies, obstetric accidents, individual maternal variations, maternal diseases, etc. Similar curves have been produced for some of the commonly used individual factors, but we are convinced that a five-point index will produce a much more accurate picture, a more composite spot graph, than produced from any single factor.

What has been said up to this point is almost strictly in the realm of pediatrics. The obstetrician is interested in this problem primarily from the point of having a concise, reasonably accurate graph from which he may determine the chance of survival of a prematurely born child. Most of these premature labors will be unavoidable in that labor cannot be stopped even with heavy sedation in their earliest phases. However, occasionally he will have charge of a maternal disease which is detrimental to mother and/or child, and he is anxious to know the probability of survival of the child if labor is induced.

We are of the considered opinion that the obstetrician's interest in premature labor must be much deeper than these academic statistical probabilities. That the mortality rate for prematurely born children has fallen markedly in the past decade is too well known to require elaboration. It is perhaps not as well known, or as freely admitted, that practically all this credit, in general, must go to the pediatrician, not the obstetrician. The modern, well-equipped, well-staffed premature nursery has apparently almost reached its irreducible premature mortality rate. Beyond a shadow of a doubt, such a nursery could make an even better showing if it were provided with better material. We

do not now have reference to material equipment, but to the quality of the premature infant delivered to that nursery. Obviously, not every prematurely born child is alive and in good condition when presented to this *milleu* for which its respiratory and gastrointestinal tracts in particular are not equipped. Certainly, the accoucheur cannot be blamed for a congenital anomaly incompatible with life nor for a breech position which is far less compatible with life for the premature infant than any vertex position. On the other hand, one does not have to dig deeper than the records of the current series to find suggestions for improving the quality of the newborn premature infant.

It has often been said that the most important phases of obstetric attention are pre- and postnatal care and that anybody can deliver the child. We cannot deny that the actual delivery is too often dramatized far beyond its true importance. Most parturients will deliver themselves spontaneously and safely within limits with major interference not often imperative when dealing with term or near term pregnancies. This is far from true when the case is one of premature labor. To be sure, proper prenatal care is the sine qua non of prophylactic treatment of premature labor. But there are few phases of obstetric care which require greater skill in plotting and greater determination in carrying out the course than does the management of premature labor and of premature delivery if the obstetrician is going to play a part in reducing the premature mortality rate.

The conduct of premature labor and delivery call for few and for rather simple principles. These are primarily concerned with the avoidance of drugs which will interfere with the initiation and continuation of respirations in the newly born premature infant and with protection of the excessively malleable fetal head. Few object to the use of even heavy sedation in the event of threatened premature labor or possibly even in apparent very early premature labor. Analgesics are all respiratory depressants and must be avoided after the onset of true labor in the period of prematurity lest resuscitation be required at delivery or stimulation necessary thereafter. Exactly the same must be said for inhalation anesthetics. The latter are unnecessary since local and regional anesthetics are admirable substitutes. We have found no mothers unwilling to tolerate premature labor without analgesia and without inhalation anesthesia if the problems are properly presented. Each has been willing to accept whatever pain may be required to afford her anticipated premature infant the best possible chance of survival. We should interject here that the pediatrician finds greatest satisfaction, when dealing with premature infants, in receiving those whose respirations have not been hampered.

One of the best means of protecting the premature infant's excessively malleable head is to preserve the integrity of the fetal membranes as long as possible, even through the second stage of labor. This is frequently impossible for premature labor is often initiated by spontaneous premature rupture of the membranes, this event having occurred in nine of the 23 cases in this series. Finally, if one is dealing with a more or less rigid lower birth canal or perineum, the use of low forceps properly applied and/or episiotomy is considered good obstetrics designed to protect the fetal head from molding beyond its safe limits. In this connection, it might be pointed out again that in case 19 of the

current series a fetus of a 30½ weeks' gestation was delivered spontaneously with episiotomy, after an eight-hour labor, the premature infant succumbing, after sixteen hours, to extensive intracranial damage.

The premature infant needs all the blood that it can bring with it into its new environment. Microcytic hypochromic anemia is common in the premature infant because of the low storage of iron and its decreased ability to metabolize iron. For this reason, it is ideal to delay clamping and cutting of the umbilical cord until the cessation of pulsations in its vessels.

Finally, the pediatrician has been impressed with the advantage of the use of chemotherapy in the newly born premature infant for he frequently, if not routinely, employs penicillin prophylactically even in the absence of any evidence of antenatal or intrapartum maternal infection. Recent bacteriological studies of the oronasal cavities of newborn infants[9] suggest the routine use of chemotherapy in all premature labors, certainly in all with ruptured membranes.

With these facts in mind, it appears that there is no obstetric-pediatric problem which requires closer cooperation between representatives of these two branches of medicine than does that of premature labor. Certainly, this is true if the obstetrician is going to play his rightful role in reducing the premature mortality rate to an irreducible level.

Conclusions

1. The absence of a universally acceptable standard for what constitutes a premature infant is deprecated.

2. Basic definitions for prematurity and for abortion are reiterated.

3. Various individual criteria for the diagnosis of prematurity are reviewed and reasons given for their inaccuracies when employed separately.

4. A five-point premature survival index is offered as a means of overcoming inaccuracies in individual criteria.

5. Application of this composite index to twenty-three premature newborns is presented.

6. Suggestions for the obstetrician's contribution in reducing the premature infant mortality rate are given. These include: avoidance of analgesia after the onset of true labor in the period of prematurity, the use of local or regional anesthesia for premature delivery, preservation of the integrity of the fetal membranes through the second stage of labor, maintenance of maternal-fetal circulation as long as possible, and the prophylactic use of chemotherapy in premature labor.

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LATE DYSTOCIA TREATED BY THE NORTON EXTRAPERITONEAL CESAREAN SECTION

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DYSTOCIA recognized late in labor or after failure of attempted vaginal delivery poses the problem of a safe termination. Transperitoneal cesarean section at this stage is hazardous because it is accompanied by a high maternal mortality from peritonitis.[1] Traumatic vaginal delivery with or without fetal destructive operations,[2] even in multiparas, has proved disastrous to the fetus, and caused a high maternal mortality.[3]

Dieckmann[4] prefers cesarean hysterectomy, despite its high maternal mortality (1 to 14 per cent), in all such "neglected" cases instead of extraperitoneal cesarean section. He claims that frequent peritoneal tears incurred during the latter operation defeat the purpose of the extraperitoneal route. On the other hand, Cosgrove and Waters[5] maintain, and quote others that hold likewise, that small peritoneal tears sustained during the extraperitoneal operation repaired before incising the uterus do not contribute to increased maternal morbidity or mortality.

There are two generally accepted methods of extraperitoneal approach to the lower uterine segment. They are the Physick-frank-Sellheim supravesical approach elaborated by Waters[6, 7] and Ricci,[8] and the Latzko[9] paravesical approach advocated by Burns.[10] Norton[11] more recently described a paravesical extraperitoneal cesarean section which simplifies and facilitates the operative technique. Its most outstanding feature is its performance by *blunt* dissection of the fascial investments of the bladder, thus reducing to a minimum injuries to that organ. It also provides for *blunt* partial separation of the peritoneal folds from the uterus and bladder, and eliminates frequent peritoneal injuries.

We followed the technique outlined by Norton[11] in the treatment of dystocia late in labor, and briefly stated it is as follows:

1. The bladder is distended with about 200 c.c. of tinted fluid. Under fractional spinal anesthesia a left paramedian incision is made through the skin and superficial fascia. The upper point of the incision is two centimeters above the visibly distended bladder, and the lower point at the pubic tubercle. The left anterior rectus sheath is incised and the left rectus muscle is detached from the midline.

2. The left paravesical space is exposed by upward and outward retraction of the left rectus muscle (Fig. 1). In this space a layer of "chicken yellow fat" is identified. Blunt dissection of the anterior fascial investments of the bladder (i.e., transversalis fascia and anterior vesical fascia) is begun at this point. The detached fascia is incised downward and to the right (Fig. 2); the starting point of this procedure is at the junction of the upper and middle third of the left border of the distended bladder, where usually the deep epigastric vessels enter the left rectus muscle (Fig. 1). This detail is important in order to prevent injury to the anterior fold of peritoneum above, if the dissection is begun higher, or to the vesical trigone and ureter, if the separation is commenced lower.

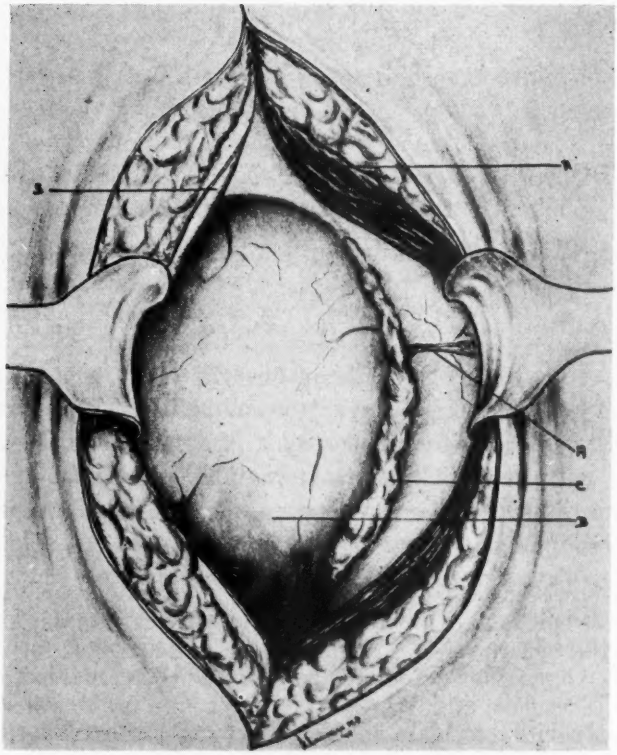

Fig. 1.—Exposure of the left paravesical space. *A*, deep epigastric vessls; *B*, distended bladder; *C*, chicken yellow fat; *S*, left rectus fascia; *R*, left rectus muscle.

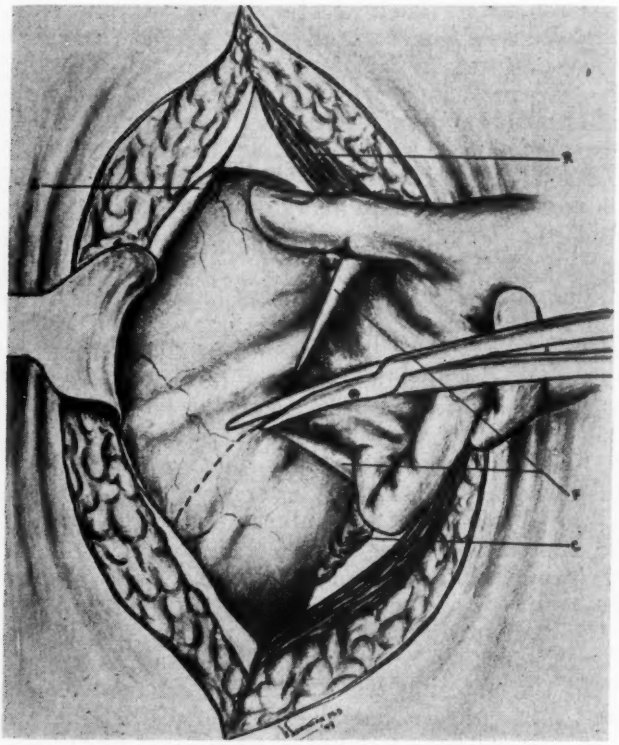

Fig. 2.—Detachment and incision of the transversalis and anterior vesical fasciae. *C*, chicken yellow fat; *S*, left rectus fascia; *R*, left rectus muscle; *F*, transversalis and anterior vesical fasciae, bluntly detached and incised downwards and to the right.

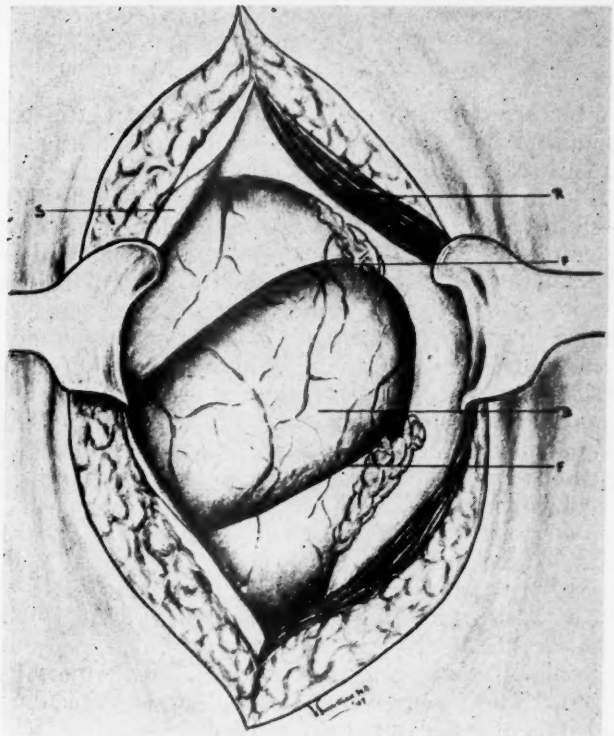

Fig. 3.—Herniation of the bladder through the cut fasciae. *B*, distended bladder; *F*, cut edges of transversalis and anterior vesical fasciae; *S*, left rectus fascia; *R*, left rectus muscle.

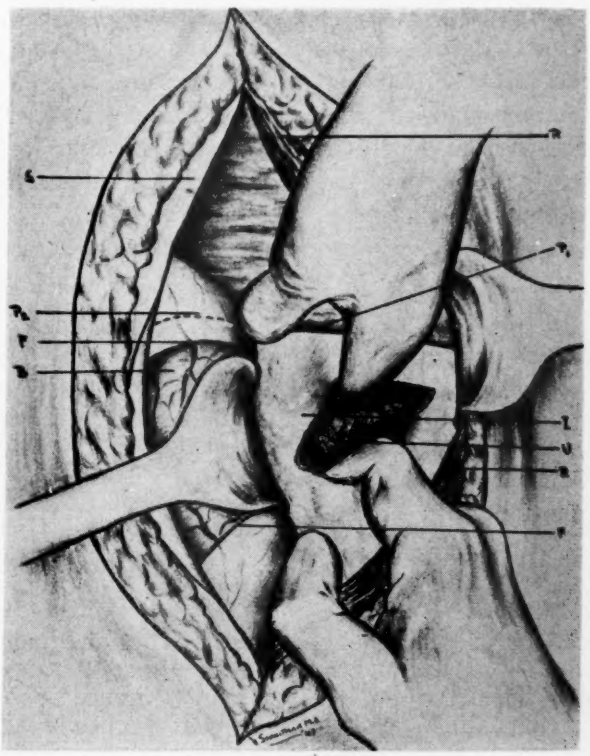

Fig. 4.—Exposure of the retrovesical triangular area. *B*, partially emptied bladder; *S*, left rectus fascia; *R*, left rectus muscle; *F*, incised transversalis and anterior vesical fasciae; P_1, posterior peritoneal fold; P_2, location of anterior peritoneal fold; *R*, *B*, P_1, outline triangular area in which *I*, the retrovesical, and periuterine fasciae are incised exposing *U*, the lower uterine segment.

3. With the bladder freed of its fasciae anteriorly permitting its herniation (Fig. 3) in its midportion and partially emptied of fluid, it is detached posteriorly by blunt dissection in the left paravesical space from the lower uterine segment sufficiently to expose a triangular area (Fig. 4). This triangular area is formed by the left rectus muscle laterally, the left margin of the partially distended bladder medially, and the posterior peritoneal fold above.

4. A small transverse incision is made in the floor of this triangle (Fig. 4) about two centimeters below the visible posterior peritoneal fold through the retrovesical and periuterine fascial layers. This incision is enlarged by the insertion of retractors and further expanded by blunt dissection to permit detachment of the peritoneum and bladder from the lower uterine segment (Fig. 5). During this procedure the bladder is gradually emptied of its fluid and pulled to the right and downward, being protected from injury by the posterior fascial sheaths. The posterior peritoneal fold is pulled upward and likewise protected from tearing by the same fascial sheaths (Fig. 5).

5. The exposed lower uterine segment is then incised either transversely in a semilunar fashion or longitudinally (Fig. 6).

6. After delivery of the fetus and placenta, oxytocics are administered. The uterus is closed with two layers of chromic sutures (Fig. 7), and all bleeding points are carefully controlled.

7. The peritoneum is inspected for perforation by permitting the patient to cough or strain. The integrity of the bladder is tested by refilling it with tinted fluid, and it is allowed to return to its original site. Finally, a cigarette drain is inserted between the bladder and the uterine incision (Fig. 7).

8. The muscle, anterior rectus sheath, superficial fascia, and skin are closed in layers with the drain emerging from the lower angle of the wound (Fig. 7).

We have performed this operation and followed the above technique in thirty-five cases (Table I). All the operations were done in instances where prolonged labor, many hours of ruptured membrane, frequent vaginal examinations, and intrapartum morbidity made the patients potentially and/or actually infected. However, we have also included in this series three patients who required abdominal delivery, but were not infected. The latter were done electively by the extraperitoneal technique to familiarize ourselves with the steps outlined above.

Table I reveals that extraperitoneal cesarean section was indicated in fifteen cases because of fetopelvic disproportion recognized late in labor. All of these patients were considered to have had ample and/or borderline pelvic measurements as evaluated by pelvic mensuration with calipers, clinical appraisal of the pelvis, and Hillis test. Antepartum x-ray pelvimetry of one patient disclosed an ample pelvis with no disproportion, and of two others with borderline measurements. Intrapartum x-ray pelvimetry exhibited one patient with an ample pelvis, one with a borderline pelvis, and three with absolute fetopelvic disproportion. In the remaining seven cases no x-ray pelvic studies were undertaken either antepartum or intrapartum. In all of these instances adequate tests of labor with unsatisfactory progress convinced us that pelvic delivery would produce poor results, and abdominal operation was decided upon.

In seven cases the operation was done for apparent cervical dystocia. In all, the pelvis was considered ample by clinical appraisal; two had antepartum and one intrapartum x-ray pelvimetry to confirm pelvic adequacy. Strong labor with lack of progress in softening and dilating the cervix, despite engagement of the presenting part convinced us that the cervix was unyielding. These patients were in labor from eighteen to forty-seven hours with ruptured mem-

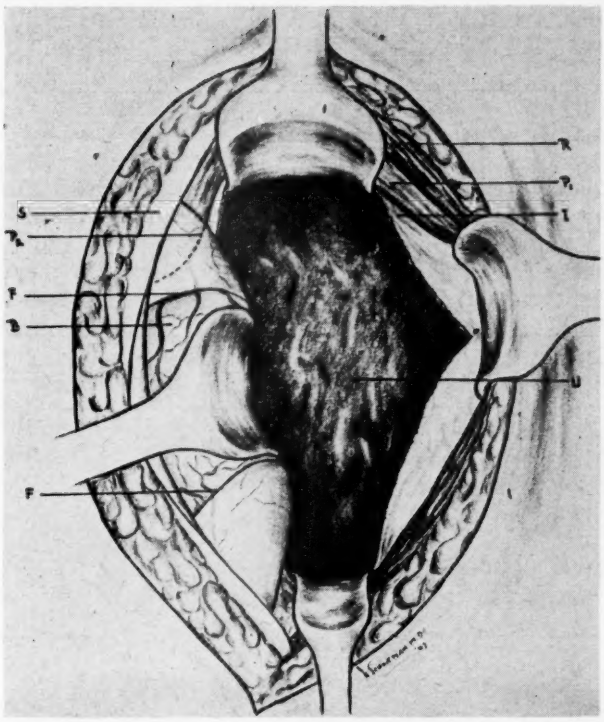

Fig. 5.—Enlargement of the retrovesical and infraperitoneal area of the lower uterine segment. *B*, retracted and almost emptied bladder; *S*, left rectus fascia; *R*, left rectus muscle; *F*, transversalis and anterior vesical fasciae; P_1, posterior peritoneal fold retracted upwards; P_2, anterior peritoneal fold attached to the fundus of the bladder and retracted to the right; *I*, retracted retrovesical and periuterine fasciae; *U*, lower uterine segment.

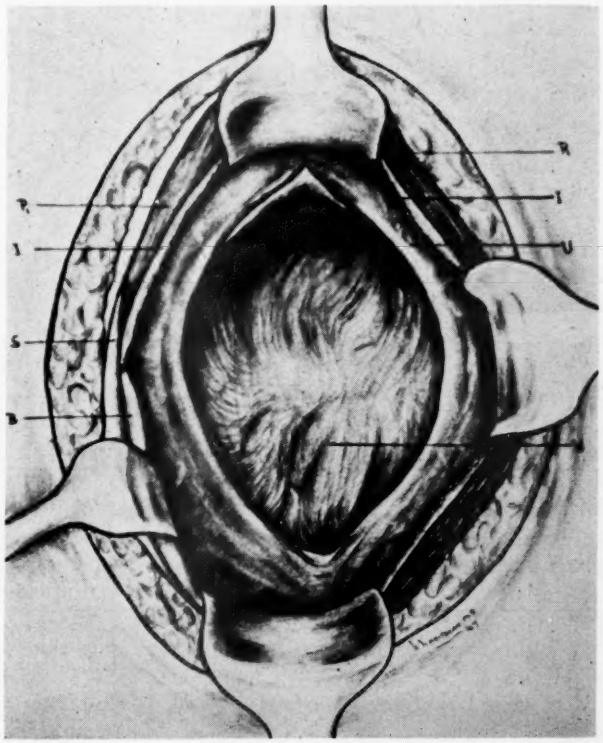

Fig. 6.—Uterine incision and delivery of the fetal head. *B*, completely emptied and retracted bladder; *S*, left rectus fascia; *R*, left rectus muscle; *I*, retrovesical and periuterine fasciae; P_1, retracted posterior peritoneal fold; *U*, longitudinally incised uterus; *H*, fetal head.

TABLE I. SUMMARY OF CASES TERMINATED BY NORTON EXTRAPERITONEAL CESAREAN SECTION

INDICATIONS	CASE NO.	PARITY		HOURS OF LABOR	HOURS OF RUPTURED MEMBRANES	INTRAPARTUM TEMPERATURE	NO. OF EXAMINATION		PREOPERATIVE VAGINAL MANIPULATION	BLADDER INJURY	PERITONEAL INJURY	HOSPITAL DAYS	RESULT		WEIGHT OF FETUS IN GRAMS
		PARA.	GRAV.				R	V					MATERNAL	FETAL	
Elective	1	0	iii	0	0	Normal	1	0	None	None	None	10	Cured	Living	2013
	2	0	i	5	0	Normal	1	0	None	None	None	12	Cured	Living	3544
	3	0	i	5	5	Normal	1	0	None	None	None	9	Cured	Living	2807
Fetopelvic disproportion	4	0	i	27	79	Normal	3	0	None	Yes	None	12	Cured	Living	3204
	5	0	i	19	19	Normal	5	1	None	None	None	9	Cured	Living	2977
	6	0	i	54	54	Normal	6	1	None	None	None	9	Cured	Living	2977
	7	0	i	5	22	Normal	1	0	None	None	None	8	Cured	Living	3402
	8	0	i	35	35	Normal	7	0	None	None	None	10	Cured	Living	2693
	9	0	i	38	38	Normal	2	0	None	None	None	7	Cured	Living	4196
	10	0	i	41	10	Normal	9	0	None	None	None	8	Cured	Living	2608
	11	0	i	29	26	Normal	9	1	None	None	None	12	Cured	Living	4366
	12	0	i	28	1	Normal	7	0	None	None	Yes	9	Cured	Living	2920
	13	0	i	20	14	Normal	4	0	None	None	None	10	Cured	Living	3175
	14	0	i	53	20	Normal	9	0	None	None	None	10	Cured	Living	3345
	15	0	i	21	17	Normal	6	2	None	None	None	9	Cured	Stillborn	2807
	16	0	i	36	33	Normal	8	1	None	None	None	12	Cured	Living	3147
	17	i	ii	19	8	Normal	3	0	None	None	None	13	Cured	Living	4253
	18	0	i	6	48	Normal	3	0	None	None	None	7	Cured	Living	3090
Cervical dystocia	19	0	i	41	41	102.2° F.	10	1	None	None	None	10	Cured	Stillborn	2977
	20	0	i	28	9	Normal	6	2	Amniotomy	None	Yes	10	Cured	Living	4309
	21	0	i	30	54	101.0° F.	7	1	None	None	None	8 hr.	Died	Living	3459
	22	0	i	17	17	Normal	5	3	Catheter Induction	None	None	8	Cured	Living	3657
	23	0	i	47	47	103.2° F.	9	1	None	None	None	10	Cured	Living	3175
	24	i	iii	35	35	Normal	4	1	None	None	None	12	Cured	Living	2608
	25	iii	v	36	35	Normal	10	2	None	None	None	16	Cured	Living	3317
Uterine inertia	26	0	i	28	36	Normal	2	2	None	None	None	10	Cured	Living	3544
	27	0	i	42	42	Normal	10	1	None	None	None	8	Cured	Living	2637
	28	0	i	56	26	102.4° F.	8	1	None	None	None	11	Cured	Living	3175
	29	0	i	160	160	Normal	3	3	None	None	None	13	Cured	Living	3004
	30	0	i	60	60	101.8° F.	9	1	None	None	None	8	Cured	Living	2240
Malpresentation and malposition	31	0	ii	0	18	Normal	1	0	None	None	Yes	12	Cured	Living	3033
	32	i	iii	9	33	Normal	7	0	None	None	None	9	Cured	Living	3232
	33	0	i	61	61	Normal	6	2	None	None	None	14	Cured	Living	2495
	34	0	i	48	48	101.6° F.	1	1	None	None	None	9	Cured	Living	3231
Failed forceps	35	0	i	16	2	Normal	5	1	Failed foceps	Yes	None	12	Cured	Stillborn	3090

branes for that many or even more hours (maximum fifty-four hours). Three patients (Cases 19, 21, and 23, Table I) had elevated intrapartum temperatures. The other four patients were considered infected because of numerous rectal and vaginal examinations or vaginal manipulations. In Case 20 membranes were ruptured artificially, and in Case 22 labor was induced for pre-eclampsia by insertion of catheters. Although sedation was used in most cases to prevent maternal exhaustion, the return of forceful labor pains made no appreciable progress in cervical dilatation. In all these cases the cervix remained thick and rigid, and in no case did it dilate beyond 5 cm. In one patient (Case 25) the maximum cervical dilatation obtained was 3 cm., despite thirty-six hours of strong labor and ruptured membranes for thirty-five hours. This patient was a multipara who had a previous uterine suspension and trachelorrhaphy.

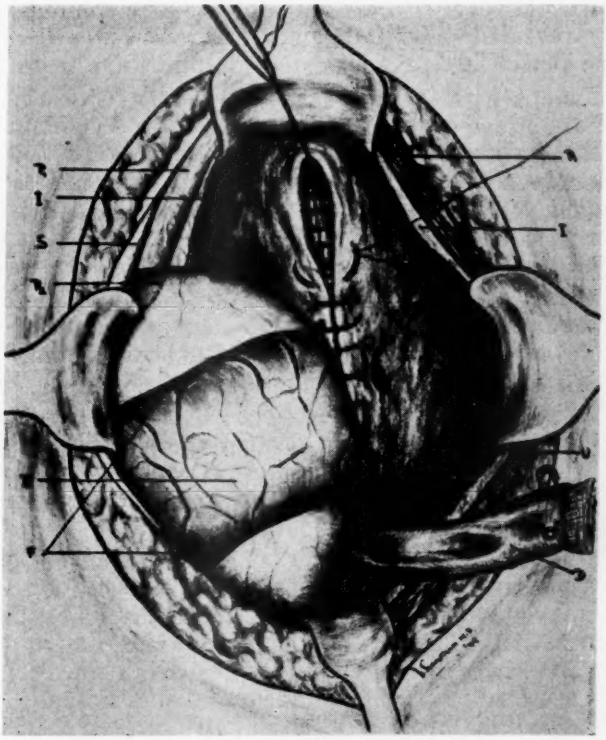

Fig. 7.—Uterine closure, testing integrity of bladder, peritoneum and insertion of drain. *U*, uterus being closed in two layers; *B*, refilled bladder; *F*, Transversalis and anterior vesical fasciae; *S*, left rectus fascia; *R*, left rectus muscle; P_1, posterior peritoneal fold; P_2, anterior peritoneal fold; *I*, retrovesical and periuterine fasciae; *D*, cigarette drain.

There were five instances of uterine inertia. Four of these patients were considered to have no fetopelvic disproportion by clinical means and pelvic mensuration done ante partum. In the fifth patient fetopelvic adequacy was assured by x-ray pelvimetry. Labor lasted from twenty-eight hours to one hundred sixty hours, and the membranes were ruptured twenty-six hours to one hundred sixty hours. In all these cases dilatation of the cervix reached from 2 to 7 cm. In three cases the presenting part was not completely engaged, and in two instances the presenting part was at the ischial spines at the time of operation. Two of the patients (Table I, Cases 28, 30) had elevated intrapartum temperatures, and the other three were regarded as potentially infected.

In four cases operation was done for malposition. These were expected to correct themselves spontaneously with continued labor and time. After

many hours of watchful expectancy correction did not occur. There were two brow presentations, one of which was in labor sixty-one hours with ruptured membranes for a similar length of time. The other brow presentation was forty-eight hours in labor with ruptured membranes occurring at the onset of labor. Both of these patients had reached 4 cm. dilatation, the presenting part was not completely engaged; one patient had an intrapartum temperature of 101.6° F. (Case 34, Table I). There was one case of transverse presentation (RScA, Case 31, Table I) in which the membranes were ruptured for eighteen hours and no labor had ensued. One patient had compound presentation (head and hand) discovered at operation. This was a multipara with unengaged vertex after thirty-three hours of ruptured membranes, nine hours of strong labor, and no progress in cervical dilatation above 3 cm. This patient previously had a breech delivery with difficulty of the aftercoming head. Although x-ray pelvimetry revealed pelvic adequacy, operation was decided upon when no descent of the presenting part occurred, despite nine hours of strong labor.

Failure of forceps with intrapartum fetal death (Case 35, Table I) which occurred during attempted vaginal delivery led us to terminate labor by extraperitoneal cesarean section rather than by a fetal destructive operation. This was a primipara who, after sixteen hours of labor and two hours of ruptured membranes, became fully dilated with the presenting part below the spines. After restoring this patient and putting her in good condition for surgery, she was delivered by the extraperitoneal route with a satisfactory maternal result.

The bladder was injured twice, or in 5.7 per cent of the cases. The rent was repaired immediately. The bladder was kept continuously empty and dry by suction with a retention catheter and a Stedman[12] pump for seven days postoperatively. Healing was complete after that time, and voiding was spontaneous. No urinary fistulae resulted.

The peritoneum was accidentally opened there times, or in 8.5 per cent of the series. This was closed with a simple ligature tie without suturing the peritoneal tear before the uterine cavity was opened. These injuries occurred only early in our experience with this operation.

The uterine cavity was entered in nineteen instances by a longitudinal incision and by a semilunar transverse incision in sixteen instances. The choice of the incision remains with the operator, depending upon conditions prevailing at the time of operation. There is less bleeding when the transverse semilunar incision is used, and there is less chance of injury to the peritoneal fold as a result of traction upward to permit an adequate longitudinal incision. In some instances the longitudinal incision is absolutely necessary. This is especially true when a constriction ring exists as in Case 29, Table I. Incising parallel to a constriction ring as in transverse semilunar incision makes for great difficulty in delivering the fetus.

There were three stillbirths in this series. One was a known fetal death prior to operation after failure of forceps. In one, the fetal heart sounds were slow (80 per minute) before operation after prolonged labor in a case of absolute fetopelvic disproportion discovered late in labor. The third stillbirth occurred in a patient with pre-eclampsia where the membranes were ruptured for forty-one hours with long labor, intrapartum elevated temperature, and thick meconium showing prior to operation. Upon delivery, the heart sounds were present but slow, and respirations could not be initiated. Those that survived weighed between 2,013 Gm. and 4,366 Gm. The average was 3,020 Gm.

Postoperative morbidity occurred in six patients, a rate of 17.1 per cent. Four patients were morbid for two days, one for four days, and one for five days; the remainder, or twenty-nine patients, were afebrile during their postpartum stay in the hospital.

Four patients had postoperative complications; two had excessive wound drainage, one had marked abdominal distention, and one had massive pulmonary embolism which occurred eight hours postoperative and proved fatal.

Summary

1. Employment of transperitoneal cesarean section in the treatment of late dystocia results in a high maternal mortality due to peritonitis. Vaginal delivery with or without fetal destructive operations, to avoid the above results, proves disastrous to the fetus and produces severe maternal trauma and even death. Cesarean-hysterectomy is a formidable shocking procedure late in labor, and also contributes to a high maternal mortality.

2. A knowledge of the extraperitoneal approach for abdominal delivery should be in the armamentarium of every obstetric surgeon. Its application in late dystocia is a conservative and safe method of termination of labor. The Norton paravesical extraperitoneal approach, in our hands, has proved easy to master. Its outstanding advantage is that it is performed entirely by *blunt* dissection. Very early in our experience we injured the peritoneum three times and the bladder twice. There have been no injuries to either structure since.

3. The Norton technique was employed electively in three patients to better familiarize ourselves with the landmarks and steps of the operation. It was indicated in fifteen cases for fetopelvic disproportion, in seven patients for cervical dystocia, in five instances for uterine inertia, in four cases for malposition and malpresentation, and once in a case of failed forceps.

4. There were three stillbirths. One was a known intrauterine death resulting from failed forceps. The others showed fetal embarrassment prior to commencement of the operation. The average weight of the babies delivered was 3,020 Gm.

5. The postoperative course was usually smooth. The incidence of morbidity was low. One maternal death occurred eight hours after operation from massive pulmonary embolism.

We are thankful to Doctors Graves, Siegler, and Weitzman for permission to include the cases operated upon at the Harbor, Coney Island, Madison Park, and Brooklyn Womens Hospitals.

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ADENOCARCINOMA ARISING IN AN ENDOMETRIAL CYST OF THE OVARY

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ADENOCARCINOMA arising in an endometrial cyst of the ovary is an unusually rare gynecologic finding. Sampson[15] originally reported this condition more than twenty-two years ago, but to our knowledge only one other similar case has appeared in the literature.

Since the incidence of endometriosis is high (26 to 43 per cent),[5, 8, 13] it would seem that carcinomatous change should be found more frequently. Such neoplasia has been reported in endometrial cysts of the Fallopian tube, the serosal surface of the uterus,[4, 12] and from endometriomas in the rectovaginal septum.[19, 20] Indeed one of us (D.M.G.)[3] has seen carcinoma arising in an adenomyoma of the uterus.

Sampson's[15] unique case of carcinoma arising from a benign cyst of the ovary was not associated with malignancy in the uterus or Fallopian tubes. He postulated rigid criteria for the proof of the endometrial origin of such a tumor. These were: (1) the coexistence of benign and malignant tissue in the same ovary which have the same histologic relationship to each other as in carcinoma of the body of the uterus; (2) the carcinoma must actually be seen arising in this tissue, and not invading it from some other source; (3) additional supportive evidence includes the attendance of tissue resembling endometrial stroma about characteristic epithelial glands and the finding of old hemorhage rather than fresh, since the latter can be the result of trauma accruing from surgical manipulation. These criteria are difficult to meet, since the carcinoma arising in benign ectopic endometrial tissue usually obscures and replaces it completely, thus hiding evidence of its origin. It is interesting to note that Novak and Goodall[14] accepted only one of Sampson's four purported cases of carcinoma arising from pre-existing endometrioma of the ovary. They thought that in the other three cases the malignancy most probably arose from cystadenomata present in the ovary. Teilum[17] recently described another case of adenocarcinoma arising in an endometrial cyst of the ovary.

In this connection, Graves[2] suggested that some papillary cystadenomata of the ovary are in reality malignant endometriomata growing from aberrant implants of uterine mucosa. However, he offered no supportive evidence for this assumption, Frank[1] and Meyer[9] are not convinced of such malignant transformations. Novak[11] has pointed out the similarity between some serous papillary cystadenocarcinomas to adenocarcinoma of the endometrium. He felt that this might be evidence in favor of Sampson's theory, but that it probably befitted only a small proportion of ovarian malignancies. Taylor[16] also agreed with the theory of origin of ovarian carcinoma from endometrial growths in the ovary which are similar to uterine mucosa. He was not certain, however, whether the endometrial growths represented transplanted uterine mucosal tissue or germinal epithelium, since both are closely akin and originate from celomic epithelium. Consequently he made no distinction between "endometrial carcinoma" and "germinal epithelium carcinoma" of the ovary. Norris

and Vogt[10] believe the prognosis more favorable in malignant degeneration of a benign cyst than in primary malignant tumors of the ovary.

Recently malignancies other than adenocarcinoma have been reported arising from benign endometrial cysts of the ovary.

McCullough, Froats and Falk[7] described an epidermoid carcinoma arising from an endometrioma of the ovary. Kuzma[6] reported two cases of ovarian adenoacanthoma developing in association with endometriosis of the ovary, but in only one of his cases is the evidence indisputable. Tuthill[18] described a most unusual carcinosarcoma arising from an endometrioma of the ovary. The diagnosis was based on the presence of endometrial glands and stroma in the cyst wall showing early malignant changes and resembling carcinoma of the uterine mucosa.

Our interest in this subject was stimulated by the unusual case described below. The diagnosis of adenocarcinoma arising from a previous benign endometrial implant in the ovary was arrived at only after extended study. All of Sampson's postulates were met including the subsidiary findings of old hemorrhage in the cyst wall. Thus, this case represents the third example of adenocarcinomatous transformation in a benign endometrial cyst of the ovary to be reported.

Case Report

The patient was a 42-year-old white female first seen on Feb. 13, 1947, with an asymptomatic mass in the abdomen.

Catamenia began at 13 years of age, recurred every twenty-eight days, with a three- to five-day flow. The last menstrual period was on Feb. 2, 1947. The patient was a gravida ii, para ii, with two full-term pregnancies, normal in character.

The past history revealed an essential hypertension and the removal of an ovarian cyst seventeen years previously, in another hospital. The nature of the cyst could not be determined, since the record had been destroyed.

Physical examination revealed a well-developed, well-nourished female with a blood pressure of 190/105. The abdomen showed an old well-healed midline scar. Pelvic examination revealed a parous scarred introitus. The cervix was lacerated and hypertrophied. The uterus was anterior to a large cystic mass which was fixed, nontender, and extended three fingerbreadths above the umbilicus.

The patient was admitted to the Jewish Hospital of Brooklyn for surgery on Feb. 16, 1947. Laboratory work-up revealed no unusual findings in the urine or blood.

At operation, through a midline suprapubic incision, a large cyst the size of a sixteen weeks' gestation was found in the right lower abdomen arising from the right ovary. It was posterior to the uterus and chocolate in color. Several loops of small bowel were adherent to the cyst, and the latter was firmly adherent at its lower pole to the uterus. The adhesions were separated and a supracervical hysterectomy and right salpingo-oöphorectomy was performed. The left Fallopian tube and ovary were surgically absent. She made an uneventful recovery, and was discharged on her twelfth postoperative day.

The patient was seen two weeks later, and her pelvis presented no masses other than a free cervical stump.

Pathological Findings.—Gross: The surgical specimen consisted of a misshapen uterus which had been amputated above the cervix. It measured roughly 10 by 7.5 by 5 cm. There were two subserous leiomyomas which measured up to 1.2 cm. in greatest diameter. The uterine cavity was 6.8 cm.

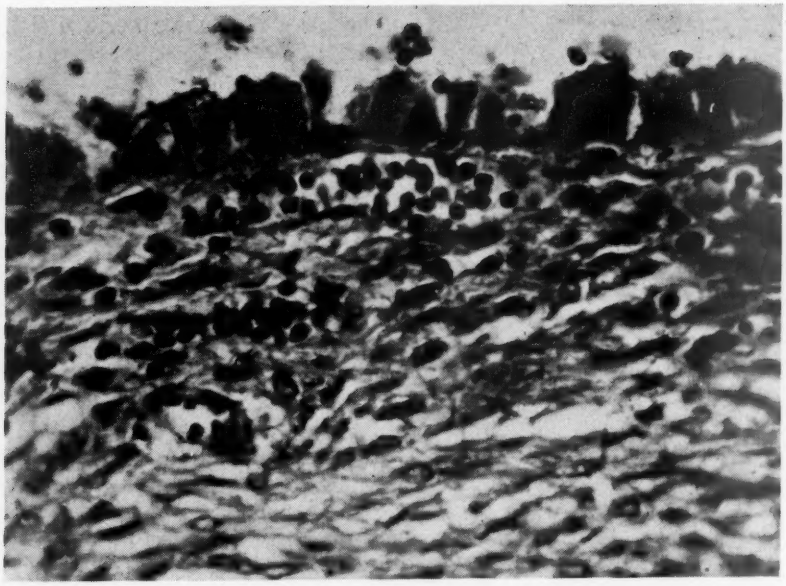

Fig. 1.—Section of cyst wall showing cylindrical lining cells (hematoxylin-eosin, ×600).

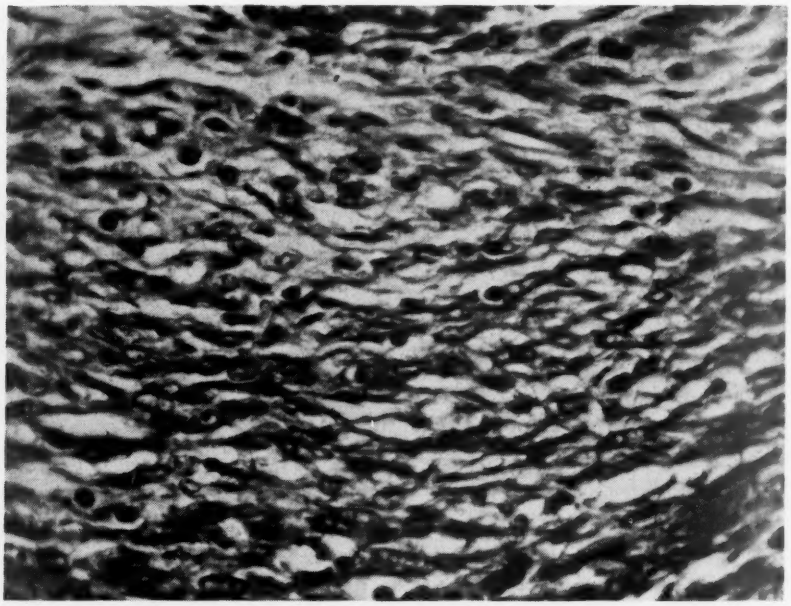

Fig. 2.—Section of cyst wall beneath epithelial layer shown in Fig. 1 showing endometrium-like stroma (Hematoxylin-eosin, ×600).

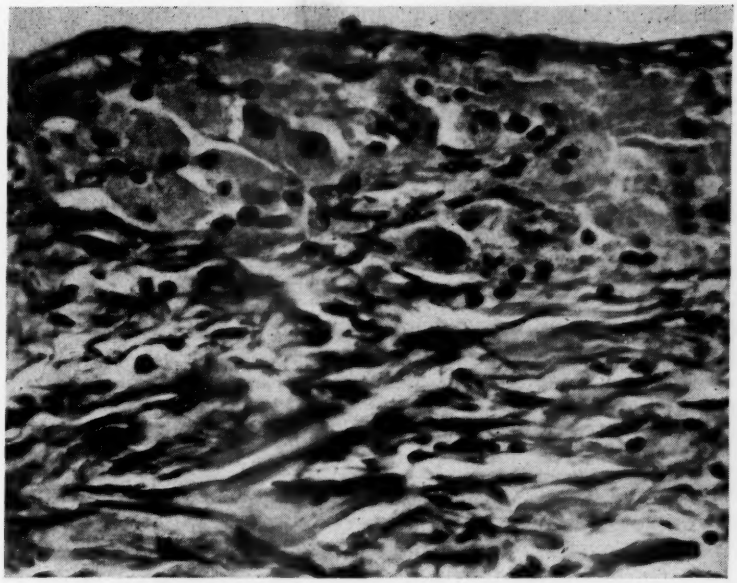

Fig. 3.—Section of cyst wall showing phagocytic cells containing blood pigment granules. Surface is denuded of epithelium (Hematoxylin-eosin, ×600).

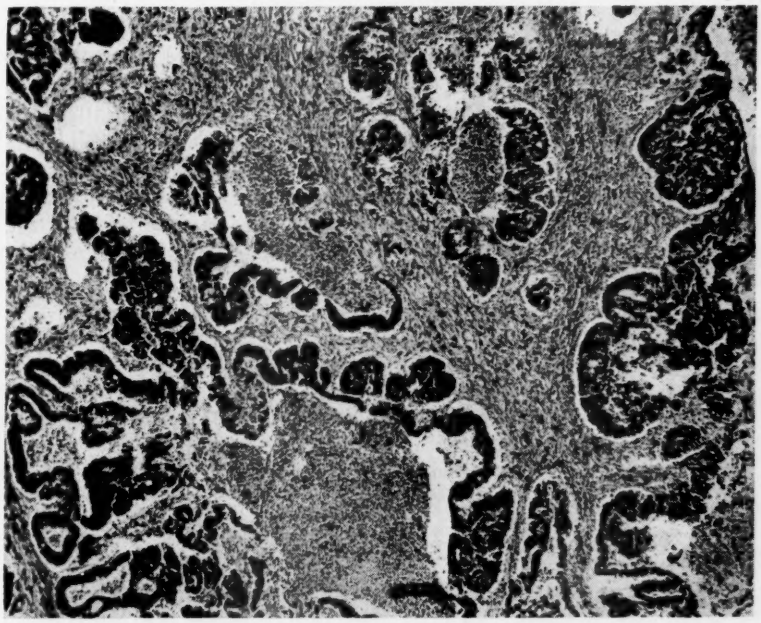

Fig. 4.—Section of adenocarcinomatous area in cyst lining (Hematoxylin-eosin, ×75).

in length, and it contained a soft polyp 2 cm. in length which was attached by a narrow pedicle; the tip was hemorrhagic. The endometrium was gray and clearly demarcated from the myometrium. The latter measured up to 2.1 cm. in thickness, and was moderately firm in consistency. Tiny lumina could be seen in the cut surfaces.

Accompanying this was an open cyst with an attached Fallopian tube. The cystic mass was said to be the right ovary, and it measured 21.3 by 11.5 cm. Its wall was gray or hemorrhagic in places, and measured up to 0.6 cm. in thickness. Lining the inner surface of the cyst was viscid dark brown material as well as soft, friable, yellow-red tissue. No normal ovarian tissue could be identified. The Fallopian tube did not appear unusual.

Microscopic: The section of the uterus showed the surface to be lined by slightly hyperplastic endometrium in the proliferative phase. Scattered throughout the myometrium were small islands of endometrial inclusions which were lined by well-preserved cylindrical cells. Most of these foci of adenomyosis were accompanied by a good amount of endometrial stroma, although in some places glandular inclusions without stroma were seen.

Section of the polyp showed it to be composed of endometrial glands supported by a delicate fibrous stroma.

Section of the Fallopian tube showed the usual corrugated lining and muscular wall. No endometrial inclusions were found.

Section of the cyst showed a thick fibrous wall which was moderately vascularized. Scattered diffusely throughout were small and large mononuclear cells as well as occasional plasma cells. A few polymorphonuclear leucocytes were also seen. The inner lining was disorganized in most places but frequently one could make out a thin layer of cylindrical cells which resembled those lining the endometrium. These were thrown into delicate corrugations and occasionally dipped down into the stroma in glandlike formation. The stroma here appeared denser and composed of thin spindle-shaped cells, similar to those appearing in the endometrium. Within the wall were also seen large macrophages containing blood pigments as well as small extravasations of blood.

Sections taken from the friable portion of the cyst showed a necrotic stroma in which were masses of atypical cylindrical cells. These cells were heaped up and hyperchromatic and the nuclei varied markedly in size and shape. Mitotic figures were present. Tumor cells extended into the lumen but did not break into the deeper layers of the cyst wall. The tumor cells often arranged themselves about lumina or along delicate stalks in glandlike or papillary formation.

Summary

1. The rarity of adenocarcinoma arising in an endometrial cyst of the ovary is noted.

2. The literature and requirements for the proof of an endometrial lesion of the ovary undergoing malignant change are reviewed.

3. A case presenting all the criteria for adenocarcinoma arising in an endometrial cyst of the ovary has been described.

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555 PROSPECT PLACE

Addendum

Since this manuscript was submitted for publication, an additional report on this subject has been published. Emil Novak (*J. Mount Sinai Hosp.* **14**: 529, 1947) describes one case of this type.

THE IMMEDIATE POSTPARTUM PERIOD AS A FOURTH STAGE OF LABOR

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THE immediate postpartum period is defined as that interval after the expression of the placenta unto complete reaction of the patient to the delivery, including a satisfactory contraction of the uterus without excessive bleeding. It is difficult to state precisely when labor begins and when it ends. However, no significant puerperal changes occur until the patient has reacted to the delivery.

The duration of the immediate postpartum period, hereafter also referred to as the fourth stage of labor, will vary from the traditional hour in the average normal patient to many hours if abnormal events occur (see case reports).

Can the immediate postpartum period be properly regarded as a stage of labor? It has distinct clinical anatomic, physiologic, and pathologic characteristics which are a denouement or anticlimax to the other three stages. The inclusion of this period in the definition of labor seems justifiable, although it is customary to consider it as the beginning of the puerperium.

Some authors, including Busey, King, and Jewett, have included this period in their definition of labor. They regarded labor as having ended when the uterus became firmly contracted. DeLee included the early regressive changes in the puerperium in his definition of labor. Stander states that the hour following delivery is just as important as the actual third stage, and that *these two periods* are more dangerous to the mother than the other stages of labor.

Modern obstetric practice includes certain procedures after delivery that modify the classical concept of labor. These practices were uncommon a hundred years ago when labor ended with delivery of the placenta. Today, obstetric anesthesia permits the immediate repair of lacerations and episiotomies after expression of the placenta. Oxytocics are given. On occasion, the uterus is explored and packed. These events take place in the delivery room as a part of the delivery and therefore of labor, and not of the puerperium. Furthermore, as the delivery is preceded by an antepartum period of uterine contractions and cervical dilatation, so it is followed by an immediate postpartum period of uterine contraction and cervical regression before actual involution begins. For these reasons, as well as the characteristics to be presented below, the immediate postpartum period easily comes within the definition of labor.

The following case reports were abstracted from the patients' records with the permission of the attending obstetricians in each instance. They illustrate the concept of the immediate postpartum period as the fourth stage of labor.

CASE 1.—Mrs. S. S., No. 434572, was a 28-year-old primigravida who had an operative (low forceps) delivery at term (3,800 Gm. infant). Analgesia was given including nembutal, scopolamine, and demerol. The delivery was performed under nitrous oxide, oxygen, and ether anesthesia. The duration of the first stage of labor was sixteen hours; the second stage lasted thirty-seven minutes; and the third stage, ten minutes. The placenta separated by the Duncan mechanism and was expressed from the vagina in the usual manner. The blood loss in the third stage was 400 c.c. Intramuscular pituitrin and ergotrate were given. After expression of the placenta, bleeding continued and ergotrate was given intravenously on three occasions. The uterus was also packed and a total of 4000 c.c. of blood was given. Oxygen was also administered. As a result of these measures the patient rallied and was sent to her room eight hours after delivery.

She regained partial consciousness. Oxygen was continued, as well as pantopon, penicillin, and other measures. Nevertheless, the patient died twenty-seven hours and thirty-three minutes after completion of the third stage of labor.

An autopsy was not obtained, but a postmortem exploration of the vagina and uterus revealed a small tear in the posterior fornix that communicated with the abdominal cavity.

The duration of the fourth stage in this case would be twenty-seven hours and thirty-three minutes. The patient never reacted completely to the delivery, and there was a pack in the uterus at the time of death, so that firm contraction was never observed.

CASE 2.—Mrs. G. G., No. 460184, was a 21-year-old primigravida, who was delivered spontaneously at term of a 3,650 Gm. infant. No analgesia was used in labor; nitrous oxide, oxygen, and ether were administered for the delivery. The duration of the first stage of labor was five hours; the second, two hours and two minutes; and the third stage, four minutes.

The placenta was expressed in the Schultze mechanism, with a blood loss of 150 c.c. Routine pituitrin and ergotrate were given intramuscularly, and the fundus was held for one hour. Thereafter, the patient was returned to her room in good condition having reacted completely to the anesthetic.

Four and one-half hours after delivery the patient passed some membranes and 250 c.c. of blood clots. A second dose of ergotrate was given. Seven hours after delivery an additional 800 c.c. in blood clots was expressed from the uterus, and thereafter the fundus remained firm, and no further bleeding occurred. A transfusion of 500 c.c. was given which was repeated in several days because the red count was still low.

The duration of the fourth stage of labor in this patient was seven hours (and not one hour as originally recorded in the labor room), counting from the time the placenta was expressed until the uterus remained firm with no excessive bleeding.

CASE 3.—Mrs. A. D., No. 281078, para i, gravida ii, was delivered spontaneously at term of a 3,500 Gm. infant after a precipitate labor. The duration of the first stage was eight hours; the second, fifteen minutes; and the third, four minutes. The total blood loss was 30 c.c. No analgesia or anesthetic was required. The uterus was held for an hour after delivery, and it remained firm.

This patient had a fourth stage of an hour's duration, the conventional period of time for holding the fundus. Most obstetric cases will fall into this category.

Historical

Leishman (1875) credits Desormeaux (1778 to 1830) with the time-honored classification of labor into three stages. Desormeaux was the successor to Baudeloque at the University of Paris in 1811. There is some precedent for dividing labor into four stages. Samuel Bard (1808) did so in the first American textbook published in America. He considered the third and fourth stages as the expulsive and placental periods. Smith (1858) in England and Edgar (1907) in America both described a preliminary or preparatory stage in addition to the classical description. Milne (1884) said that, while some authors taught four and even five stages, he preferred to use three. All modern textbooks divide labor into three stages.

Madame Bourgeois (1609), the first midwife to write an obstetric textbook, limits the immediate postpartum period to one or two hours, and describes its management as follows: "As soon as the woman is delivered after a hard labor, she must be put in the skin of a black sheep which has been flayed alive. This is applied to the back. To the belly is applied the skin of a hare which has also been flayed alive. . . . This chases away melancholic blood. In winter these remedies must be kept on two hours and in summer one hour." Chapman agreed with this!

DeLee (1913), stated that the accoucher should remain in the house for an hour, and before leaving should assure himself on the following seven points: i.e., uterus, hemorrhage, placenta, bladder, tears, infant, patient.

Stander (1936), in addition to the statement referred to above, also said that the hour following delivery was just as important as the actual third stage from a practical point of view.

Morris Leff (1939) defined and described the management of the third and fourth stages of labor, the latter constituting the immediate postpartum period. Leff considered the fourth stage at an end when the patient had been returned to her room. This extent of time is insufficient as shown by Case 1. The same author (1945) described the effect of oxytocics on the physiologic picture of the third and fourth stages. Greenberg (1946) gave his views on the physiology of the contractile and hemorrhagic phases of a fourth stage, which was limited to the first postplacental hour. This period of time is sufficient for the average case (see Case 3) but not for abnormal cases as described in Cases 1 and 2.

The present article is a presentation of a definition of the immediate postpartum period, and a description of its clinical, anatomic, physiologic, and pathologic characteristics.

Discussion

The prevailing concepts of the immediate postpartum period need no revision in order to include it as a part of the process of labor. One need only to reflect on the clinical, anatomic, physiologic, and pathologic characteristics of the immediate puerperium to realize that this period is truly a stage of labor.

The *clinical* aspects of this period include the following: effects from analgesia or anesthesia; estimating or measuring the blood loss; postpartum administration of oxytocics; repairing lacerations or episiotomy; holding the fundus for an hour after delivery; checking the pulse, respirations, and blood pressure; examining the placenta; caring for the infant (tying the cord, silver nitrate, weight, etc.); sometimes removing membranes or a succenturiate lobe;

exploring the uterus or packing it; transfusions; etc. When the patient has completely recovered from the effects of labor and delivery, including analgesia and anesthesia used in labor, with the uterus remaining firmly contracted without excessive bleeding, the fourth stage of labor may be considered clinically at an end.

The *anatomic* characteristics include the firm, thick fundus or the active segment of the uterus, and the thinner, loosely contracted lower uterine segment and cervix, or passive segment. The placental site consists of compressed uterine glands in the basal layer (Gebhardt's glands), which are invaded by chorionic giant cells according to J. W. Williams, whose article on the subject was published posthumously in 1931. He stated that it was often impossible to detect the placental site grossly in fixed specimens removed after cesarean section.

Physiologic characteristics include the alternate contraction and relaxation of the uterus after completion of the third stage. The placenta has separated along Nitabuch's layer between the placenta and the decidua vera. Festooning and shortening of the uterine muscle fibers reduce the size of the uterus as well as the placental site. Bleeding may continue after the placenta has been expressed. Extreme relaxation or uterine atony at this time may result in postpartum hemorrhage and death, as shown in Table I.

The *pathologic* aspects of the immediate postpartum period constitute important complications. These include: retained membranes, cotyledons, or succenturiate lobes; rupture or inversion of the uterus; vaginal lacerations; postpartum chill; postpartum hemorrhage; convulsions of eclampsia; cardiorespiratory failure; drug or anesthetic reactions, and aspiration pneumonia.

The various causes of maternal death occurring in the immediate postpartum period serve to make this stage of labor doubly significant. A total of 88 maternal deaths occurring at the New York Lying-In Hospital from 1932 to 1945, includes 28 patients (32 per cent) who died during the immediate postpartum period of labor. The causes of death in these patients are given in Table I. Lafferty has reported that 33 per cent of the maternal deaths in Philadelphia occurred within the first twenty-four hours of delivery.

TABLE I. CAUSES OF DEATH IN THE IMMEDIATE POSTPARTUM PERIOD OF LABOR

Postpartum hemorrhage	12
Cerebrovascular accident	5
Cardiac failure	4
Anesthesia	2
Aspiration pneumonia	2
Rupture of uterus	2
Transfusion reaction	1
Total	28

Summary

Definition.—The immediate postpartum period may be defined as the interval after expression of the placenta to a satisfactory reaction of the patient to the delivery including a firmly contracted uterus without excessive bleeding.

The duration will vary from the traditional hour, under normal conditions, to many hours when abnormal conditions arise. Ordinarily, the period will be of sixty minutes' duration, the conventional interval of time for holding the fundus. The concept was illustrated with case reports.

This period has definite clinical, anatomic, physiologic, and pathologic characteristics that justifies its inclusion in the definition of labor as a separate fourth stage. These characteristics are the anticlimax to the preceding three stages of labor.

Twenty-eight, or one-third of a total number of eighty-eight maternal deaths occurred, or were recognized, in the immediate postpartum period. The commonest cause was postpartum hemorrhage. Emphasis should be placed on this stage by recording its events as part of the labor history.

The characteristics of the immediate postpartum period as a stage of labor should be publicized nationally. It is expected that such a program will serve to reduce the number of preventable maternal deaths occurring during the fourth stage of labor.

The exact definition and connotation of the immediate postpartum period as a fourth stage of labor will depend on additional observations and recorded reports, as was the case with the other three stages. Meanwhile, there need be no doubt that this period is truly a part of labor.

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PREMATURE QUADRUPLETS

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THE quadruplets whose birth is reported here are the children of Mr. and Mrs. C. H., Jr., of Baltimore, Maryland. The father is an American of English ancestry, born in 1920 and the mother an Englishwoman, also born in 1920, who came to the United States as a war bride. There is no history of multiple births on either side of the family. The couple have an older child, a boy 1½ years of age at the time of the birth of the quadruplets. This previous pregnancy ran a normal course, and the child has grown and developed normally.

On July 20, 1946, when the patient was two months pregnant (with quadruplets, as was afterwards ascertained), she had an attack of acute appendicitis. A gangrenous appendix was removed through a McBurney's incision. The ovaries could not be seen. Recovery was rapid and uneventful.

When the patient first presented herself to the obstetrician (Bowyer) on September 3 for prenatal care, she had no complaints as to health and was at or near her normal weight of 135 pounds. She was Rh positive. The last menstrual period having begun May 2, 1946, the calculated date of delivery was Feb. 9, 1947. Nothing unusual was found on physical examination except that the fundus uteri was 20 centimeters above the symphysis pubis. This finding indicated that delivery would occur about Dec. 9, 1946, rather than in February, 1947 but at the time it was assumed that the patient had erred about the menstrual history.

The next prenatal visit was on Oct. 4, 1946. There were no complaints. The patient now weighed 153 pounds. The blood pressure was 124/72. There was no albumin in the urine. The height of the fundus uteri was 24 centimeters. Fetal heartbeats were not heard, but the patient stated that she felt slight fetal movements.

On Nov. 11, 1946, there were still no complaints. The blood pressure had risen to 145/88. The weight was 165 pounds, having increased 12 pounds since the previous visit. Edema of the whole body was noted. The urine showed specific gravity of 1.028, no albumin. Two fetal hearts were heard.

The patient was put to bed for one week at home with a diet of milk and sweetened fruit juices, and was given ½ oz. of magnesium sulfate daily. At the end of the week her blood pressure had dropped to 130/70; the weight had decreased 3 pounds during the week, to 162 pounds. The urine remained free of albumin; the specific gravity was 1.016.

At this time, i.e., November 18, two hundred days after the last menstrual period, an x-ray examination was made by Dr. Eugene L. Flippin, which clearly revealed a quadruple pregnancy (Fig. 1): In view of this finding, complicated with a mild pre-eclamptic condition, immediate hospitalization was advised for the duration of the pregnancy and the patient was moved to St. Agnes Hospital.

At the time of entering the hospital, Nov. 20 1946, the patient had a blood pressure of 130/80. The weight was 162 pounds. The urine was normal. Treatment consisted of a simple low caloric diet with unlimited tea. The weight,

blood pressure, intake and output of fluids, and urinary findings were recorded daily, and showed no significant changes, remaining within the range of normal single pregnancy. On December 22 the weight was 166 pounds, blood pressure 122/72.

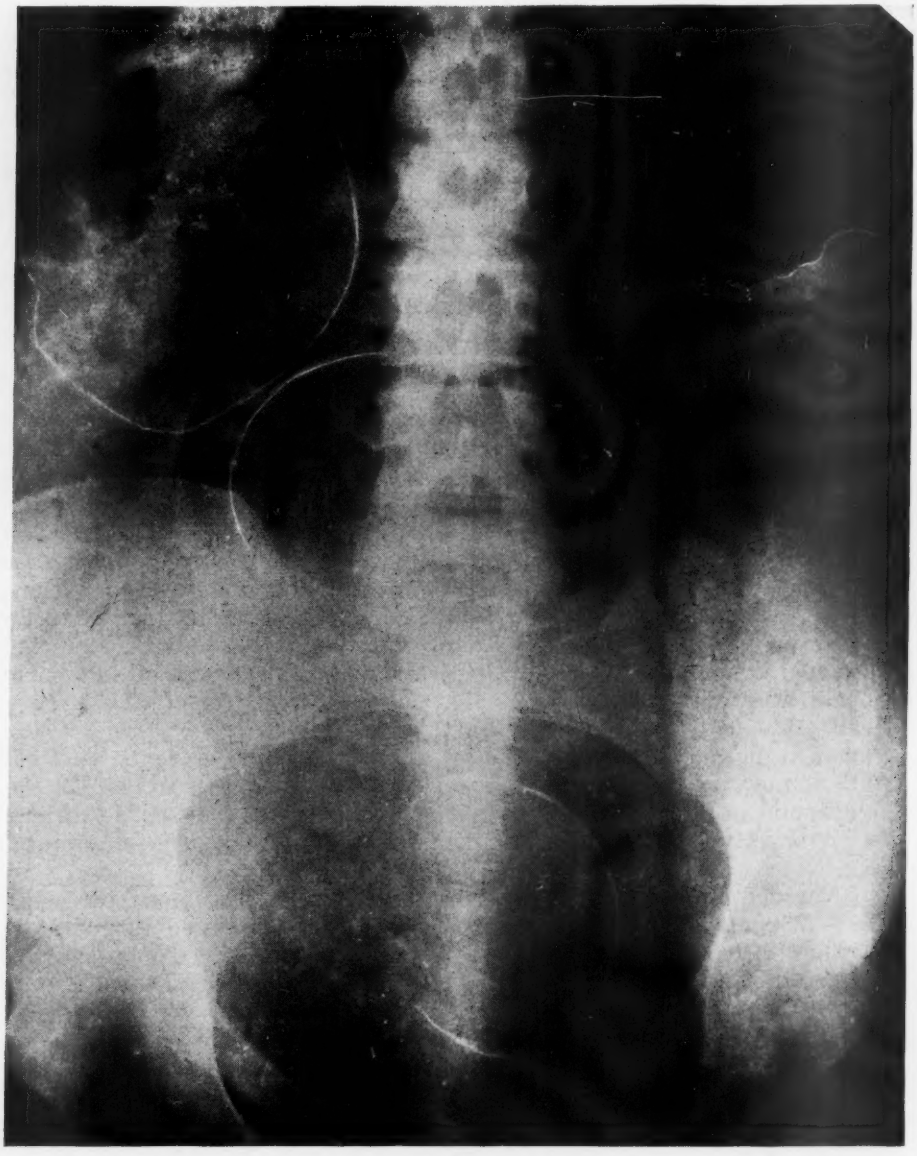

Fig. 1.—Radiograph of pelvis showing four fetal heads. The outlines of the heads have been slightly strengthened by retouching in order to make them visible in the half-tone reproduction (reduced).

At 1:00 A.M. on December 23 the patient complained of mild indigestion, which persisted for seventeen hours. Repeated rectal examinations during this time failed to reveal a presenting part, although there was a slow dilatation of the cervix with bulging of the membranes through the cervical canal. The contractions could not be timed. At 6:30 P.M. the patient said something was hanging from her vagina. This proved to be an intact amniotic sac. She was

Fig. 2.

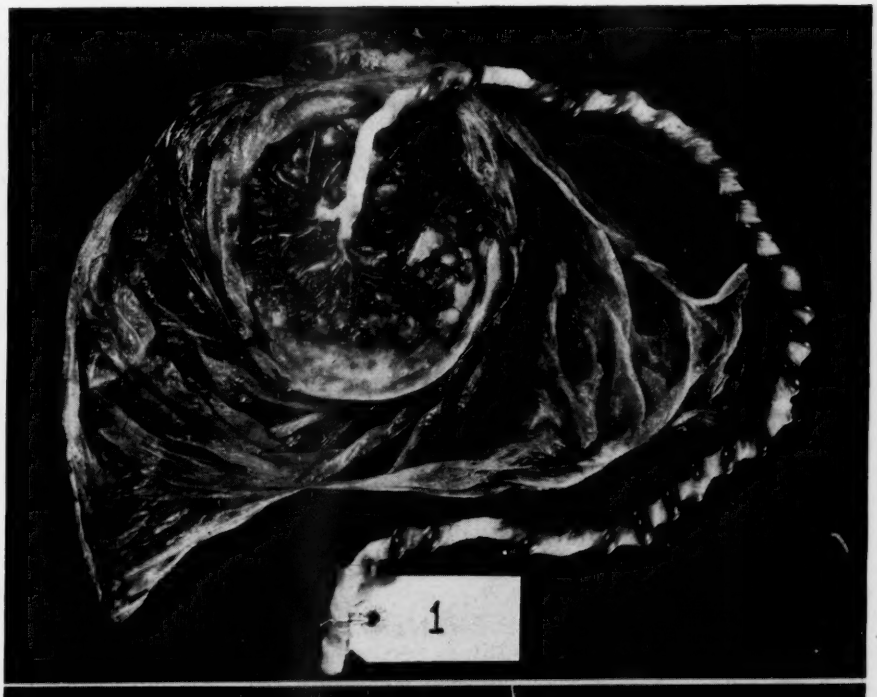

Fig. 3.

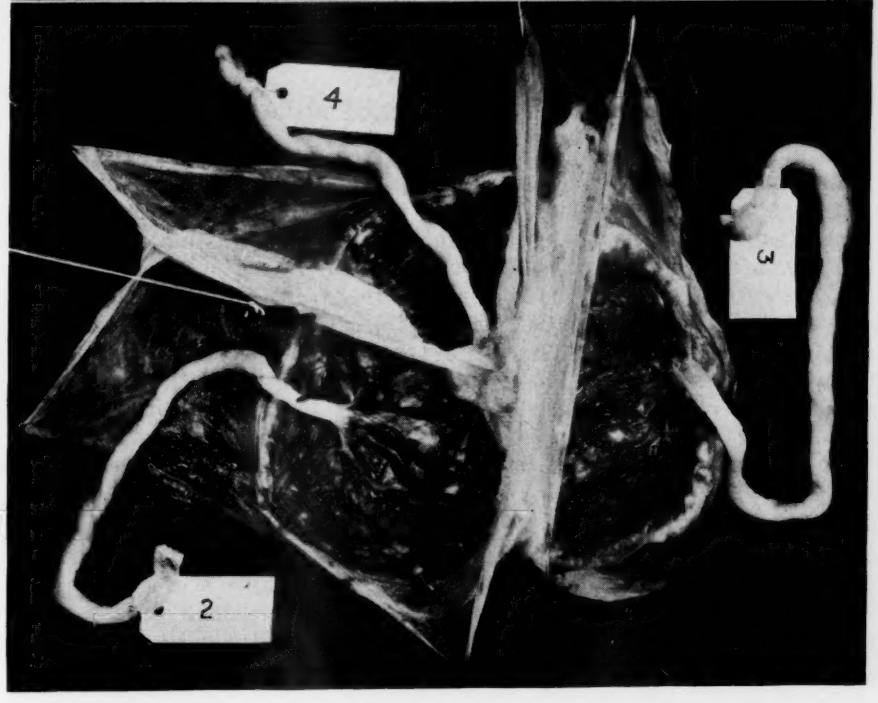

Fig. 2.—Placenta (No. 1) of infant A.
Fig. 3.—Fused placentas and membranes of infants B (2), C (3), and D (4).

moved to the delivery room, the amniotic sac was artificially ruptured, and in five minutes the first baby was born. Spinal anesthesia was to have been employed, but because of the rapidity of events, it was not administered and the labor was completed with no anesthetic and without serious pain. Delivery took place in the following order, and was spontaneous except that in each case the amniotic sac was artificially ruptured.

A. Left occipitoanterior, male, 6:45 P.M. The corresponding placenta was delivered at 6:50 P.M.
B. Left occipitoanterior, male, 7:04 P.M.
C. Right sacroanterior, male, 7:34 P.M.
D. Right occipitoanterior, female, 7:40 P.M.

The three placentas of the three last-born infants were delivered as a fused mass at 7:45 P.M.

The four infants were marked, as usual, with identification tags, and each cord, as soon as it presented itself, was tagged with a number, 1, 2, 3, and 4, corresponding respectively to infants A, B, C, and D. This precaution would have been essential for subsequent embryologic and anthropometric studies, had the case turned out to be one of mixed single-ovum and multiple-ovum gestation.

The patient remained in the hospital sixteen days after parturition. Her convalescence was uneventful in every respect and she was walking about in ten days.

The weight of the infants at birth was A, 1,320 Gm.; B, 1,740 Gm.; C, 1,920 Gm.; D, 1,590 Gm. The children have thrived under pediatric care with the usual care and feeding given premature babies. At the end of April, 1947, four months after birth, they were all well and each weighed in excess of 11 pounds (5,000 Gm.).

Description of the Placentas and Membranes

The placentas and membranes were given to the embryologist (Corner) about one half hour after delivery. These specimens, with the records and photographs, are filed in the Carnegie Embryological Collection under the serial number 8448. The placenta of infant A, which was delivered immediately after the infant, and before the birth of infant B, measured 14 by 13 cm. It weighed after several days in 10 per cent formalin, 477 Gm., and must therefore have weighed about 455 Gm. in the fresh state. This placenta was eccentrically circumvallate, i.e., at one side (seen at the top of Fig. 2); the membranes were attached about 3.5 cm. inside the margin of the placental tissue, whereas at the other side they were attached to the placental border. The "vallation" or elevation of the extra-chorionic zone of the placenta was not over two millimeters above the level of the placenta within the membranes.

Placentas 2, 3, 4, and the corresponding membranes were firmly fused to each other, as seen in Fig. 3. When examined fresh at the laboratory it was erroneously thought that the septum between sacs 2 and 4 was thinner than the others, and that the chorion was possibly continuous over the line of fusion of the amnions. Indiscreet mention of this possibility to a reporter led to inaccurate newspaper reports which were widely circulated. It was thought best not to investigate the fused membranes for fear of tearing them. The three sacs were therefore packed lightly with cotton, to keep them distended, and the whole mass was placed in 10 per cent formol.

After fixation it was clearly apparent that there were three separate chorions, which were firmly affixed but could be separated by pulling them apart.

The three placentas were fused to such an extent that they could not be separated without tearing placental tissue, although three separate masses were more or less clearly demarcated by depressions on the maternal surface.

The following measurements and characteristics of the placental components were noted:

The total weight, after several days in formol, was 1,385 Gm. The weight when fresh must have been about 1,320 Gm., or slightly more than three times the weight of the single placenta corresponding to infant A. The dimensions were:

No. 2, 18 by 11.5 cm., cord slightly eccentric;
No. 3, 17 by 11 cm., cord very eccentric, attached near margin of the placental mass;
No. 4. 15 by 11.5 cm., cord very eccentric, attached near center of the placental mass.

These findings indicate that the four infants developed from four separate fertilized ova and that three of them (B, C, D) became implanted so closely together that their placentas began to fuse, and hence to modify each other's form, relatively early in pregnancy.

Summary

A case of fraternal quadruplets, three boys and one girl, diagnosed by x-ray at two hundred days (menstrual age) and born prematurely at 235 days.

NONFATAL PULMONARY EMBOLISM BY AMNIOTIC FLUID CONTENTS WITH REPORT OF A POSSIBLE CASE*

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STEINER and Lushbaugh,[1] in October, 1941, presented a syndrome entitled "Maternal Pulmonary Embolism by Amniotic Fluid" as one cause of unexplained shock and unexpected death in obstetrics. In their original monograph they demonstrated the presence of emboli in the lungs of obstetric patients at autopsy, the emboli being due to particulate matter contained in the amniotic fluid. These authors then produced experimentally a similar clinicopathologic picture in dogs and rabbits by the intravenous injection of suspensions of particulate matter obtained from amniotic fluid. Their original paper[1] gave the clinical histories and pathologic findings in eight human patients; a later publication[2] by the same authors added two more cases to their series. All ten cases ended fatally, the diagnosis being made only at autopsy. During the preparation of this paper a case report appeared in the February, 1947, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY by Hemmings,[3] adding to the literature the eleventh case of fatal maternal embolism from amniotic fluid contents, proved by autopsy findings. To date no case report can be found in which the *clinical* diagnosis of this syndrome had been made either preceding or following the death of the patient, in all instances it seems to have been an unexpected finding at necropsy. Furthermore, we have been unable to find a single recorded instance of recovery of a patient suspected to have had this type of embolus.

A young woman who went into profound shock during parturition was recently delivered on the obstetric service of the Sinai Hospital. Her clinical course, physical findings, and roentgenologic evidence strongly suggest that her case may be an instance of pulmonary embolism by amniotic fluid contents which *did not* end fatally. The case history follows.

Case Report

Mrs. M. L. A., an 18-year-old white primigravida, registered in the prenatal clinic on May 5, 1946. Her past history was negative, except for pneumonia at the age of four years. There was no history of previous rheumatic fever or heart disease. Expected date of confinement was Jan. 12, 1947. Physical examination at registration revealed systolic murmurs at both the apex and base, which were not transmitted and considered to be functional. Blood pressure was 128/62; height, 62 inches; weight, 102½ pounds (nonpregnant 99 pounds); blood: S.T.S. negative, Group O, Rh positive. X-ray of chest on May 13, 1946, revealed: "Heart is average size and shape. Diaphragms regular. Lung fields are clear."

*Presented at a meeting of the Baltimore Obstetrical and Gynecological Society March 14, 1947.

Patient was seen regularly; and her course was uneventful. She had no cardiac signs or symptoms, and it was not deemed necessary to send her to the Obstetric-cardiac clinic for investigation of her murmurs. On Dec. 10, 1946, the fetus was in breech presentation, and she was seen at weekly intervals thereafter. X-ray pelvimetry on Jan. 7, 1947, revealed: Single fetus, breech presentation. Obstetrical conjugate 11.4 cm. Transverse of inlet 13.0 cm. Bispinous 11.2 cm. Bituberous 11.2 cm. Adequate gynecoid pelvis." She was seen in the prenatal clinic on Jan. 28, 1947, the fetus still in breech presentation, cervix soft, thick, and 2 cm. dilated. Blood pressure was 170/100 and weight 117 pounds, a gain of 3 pounds in one week, and a total gain of 18 pounds during pregnancy. Urine was negative. Because of rise in blood pressure, sudden gain in weight, three weeks postmaturity, engagement of the presenting part at the spines, and favorable cervix, admission for induction was advised.

She was admitted at 8:15 A.M. Jan 29, 1947, not in labor, with a blood pressure of 140/80. A routine medical induction with 1 ounce castor oil, a soapsuds enema, and pitocin was given. The latter was started at 9:15 A.M. on January 29, receiving ½ minim of pitocin for two doses and 1 minim for four doses, each injection given intramuscularly at twenty-minute intervals. Irregular uterine contractions began at 11 A.M. Pitocin was completed at 12:05 P.M. Uterine contractions became regular at 1:00 P.M., occurring every five to seven minutes. Labor progressed slowly although contractions were good, and 50 mg. of demerol and grain $\frac{1}{150}$ of scopolamine intravenously were given at 6:30 P.M. Scopolamine, $\frac{1}{150}$ grain intramuscularly, was repeated at 7:30 P.M. At 4:30 P.M. blood pressure was 190/100, and at 5:30 P.M. 160/100.

At 7:30 P.M. the cervix was fully dilated, fetus was presenting as a frank breech in right sacroposterior position. First stage lasted eight hours and thirty minutes.

She continued in the second stage of labor for two hours, when the breech reached the perineum and the membranes were artificially ruptured. The contents of the amniotic sac consisted entirely of undiluted meconium.

Nitrous oxide and oxygen anesthesia was started at 9:55 P.M., and the anesthetist noted that adequate anesthesia could be maintained with a minimal amount of nitrous oxide, so that at times the patient received practically pure oxygen. In spite of this, moderate cyanosis was noted by the anesthetist periodically throughout the delivery and repair.

Delivery was preceded by a deep left mediolateral episiotomy. Strong suprafundic pressure was made by the assistant (W. S.) until the operator (L. M. S.) could reach the anterior groin with an index finger. By moderate traction the breech was delivered without great difficulty. The body, arms, and shoulders followed in the usual manner. Piper forceps were applied to the aftercoming head to complete the delivery. The 6 pound 3 ounce male child was born at 10:10 P.M. Jan. 29, 1947. The second stage of labor lasted two hours and forty minutes. Ergotrate, 1 ampule, was given intravenously at 10:10 P.M., and 1 ampule of pitocin intravenously at 10:16 P.M. The placenta and membranes were expressed intact at 10:12 P.M., and it was noted that the membranes and amniotic surface of the placenta were stained a deep meconium greeen. The third stage lasted two minutes. Total labor eleven hours twelve minutes. Blood loss was estimated to be 150 cubic centimeters.

The baby appeared to be in good condition, but initial respiration and crying were slightly delayed—being two minutes fifty seconds, and four minutes thirty seconds, respectively.

Toward the end of the episiotomy repair it was noted that the blood oozing from the perineum was quite dark, and further inspection revealed mixed pallor and cyanosis of the face, and marked cyanosis of the fingernails. The pulse was

found to be hardly obtainable, rapid and thready. Blood pressure could not be obtained. Respirations were rapid, shallow, and labored. Immediate auscultation of the chest revealed both lung fields to be filled from apices to bases with coarse, moist, bubbling râles, so loud as to almost obscure the very rapid heart sounds. This occurred at 10:30 P.M., eighteen minutes post delivery.

Anesthesia was immediately stopped, 100 per cent oxygen given, patient's position changed to reverse Trendelenburg, and cardiac stimulants were ordered. Medications given were 1 ampule of digalin intramuscularly at 10:40 P.M.; 1 ampule of adrenalin intramuscularly at 10:42 P.M., 1/150 grain of atropine intravenously at 10:45 P.M. The patient was still deeply cyanotic, both skin and nails, dyspneic in spite of constant oxygen, and respirations were rapid and shallow. The diagnosis of pulmonary embolus due to meconium was ventured at this time by an attending obstetrician (W. S.) who was present. Intravenous fluids were interdicted for the time being.

From this point treatment of the patient was continued with the cooperation of the medical resident staff. Tourniquets were placed on three limbs, and alternated every twenty to twenty-five minutes. Cedilanid, 4 c.c. intravenously, was given at 11 P.M. Caffeine-sodium-benzoate, 2 c.c. intramuscularly, was given at 11:10 P.M. Pulse and blood pressure were still unobtainable. Auscultation of the heart was unsatisfactory due to the loud inspiratory and expiratory moist bubbling pulmonic râles.

For a short time the left chest cleared of râles somewhat and the apex rate was found to be 144 per minute, with definite gallop rhythm. An electrocardiogram taken at about 11:15 P.M. showed sinus tachycardia. Morphine sulfate, 1/6 grain, and atropine, 1/150 grain, were given intramuscularly at 11:30 P.M.

At 12:15 A.M., two hours post partum, blood pressure was obtainable for the first time and was 96/80. At about 12:30 A.M. a whole citrated blood transfusion was started at approximately 25 to 30 drops per minute. Cardiac rate at this time was 140 to 150. Morphine, 1/6 grain, and atropine, 1/150 grain, were given intramuscularly at 1:10 A.M. Penicillin, 60,000 units, were given every three hours. Patient was still in poor condition, with extreme cyanosis and polypnea.

At 3:00 A.M., five hours post partum, the patient was considerably improved. Gallop rhythm was still present, with a rate of 150. Two cubic centimeters of cedilanid were given intramuscularly. Patient was still getting 100 per cent oxygen on the table.

At 4:00 A.M., six hours post partum, the patient's temperature was 101° F.; pulse 120; respirations 34. Blood transfusion was completed.

At 9:00 A.M., eleven hours post partum, the patient's temperature was 100° F.; pulse 130; respirations 32. The patient was in an oxygen tent and receiving oxygen through a nasal catheter. She was very cyanotic, moderately dyspneic, and apprehensive. Both lungs filled with bubbling moist râles again, and she was coughing up frothy, watery, blood-tinged sputum. Tourniquets again were applied to limbs and 2 c.c. cedilanid were given intramuscularly.

Portable chest film showed that the heart did not appear to be enlarged. Mediastinum was not shifted. The intercostal spaces were equal bilaterally. Diaphragms were in normal position. There was an area of increased density involving the second and third anterior interspaces on the left side, and also involving the lower two-thirds of the right lung, more marked at the base of the seventh rib posteriorly. From the shape of these dense areas, infarctions could not be ruled out (Fig. 1).

At 10:30 A.M., twelve and one-half hours post partum, 300 mg. of dicoumarol by mouth and 50 mg. of heparin were placed in 500 c.c. of normal saline

solution and started by slow intravenous drip. Hematology; red blood cells, 5,250,000; hemoglobin, 16.2 Gm. (112 per cent); white blood cells, 15,000; polymorphonuclears, 93 per cent; lymphs, 7 per cent; sedimentation rate, 32.

At 2:00 P.M., sixteen hours post partum, the blood pressure was 98/80. Temperature 101° F., pulse 124, respirations 52.

At 10:00 P.M., twenty-four hours post partum, the patient took a sudden turn for the worse and became deeply cyanotic, dyspneic, and anxious. Respirations were 64; her pulse was regular, and she had an equal cardiac rate of 134. Her blood pressure was 120/100. A marked gallop rhythm was still present. Chest signs were noted as above, with scattered râles. She was raising small amounts of thin, pink, frothy sputum. Morphine, ¼ grain, and atropine, $\frac{1}{150}$ grain, were given intramuscularly, and the patient responded promptly. She fell asleep, her respirations dropped slightly, and the dyspnea decreased.

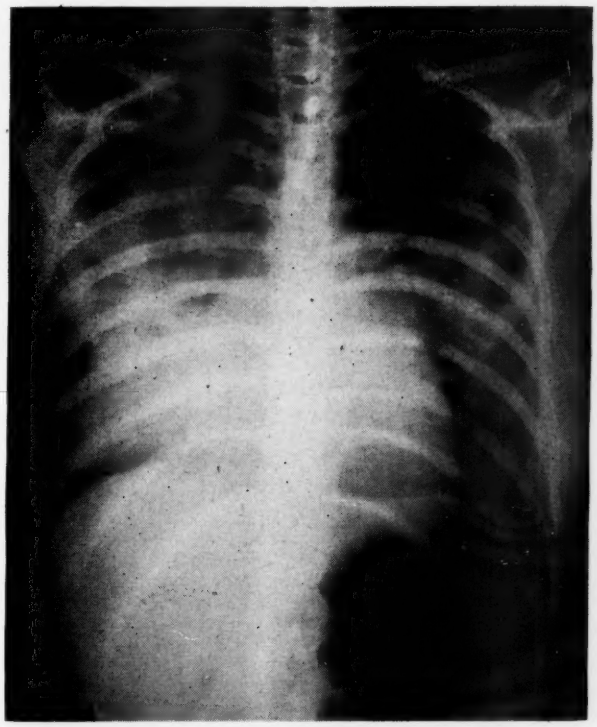

Fig. 1.—Portable chest film twelve hours post partum.

Second Postpartum Day.—At 9:00 A.M., thirty-five hours post partum, a remarkable improvement was noted in patient's condition. Her temperature was 101.2° F.; pulse was 104 and regular; respirations were 40. Gallop rhythm had disappeared. Her left chest was clear of râles. Breath sounds at right apex were still tubular. White blood cells were 12,700; polymorphonuclears, 89 per cent; lymphs, 9 per cent; monocytes were 2 per cent.

At 12:30 P.M., thirty-eight and one-half hours post partum, the patient had received a total of 200 mg. of heparin and 300 mg. of dicoumarol in twenty-four hours. Coagulation time was fourteen minutes, and prothrombin time 60 per cent of normal. Heparin and dicoumarol were discontinued.

Third Postpartum Day.—At 9:00 A.M., seventy hours post partum, the patient's temperature was normal; heart sounds were good; no gallop was present. Pulse was 90 and regular, respirations 30. Tubular breathing was less marked

in the right apex. Many fine moist râles were present. No cough or sputum was noted. Color was good, but the patient was still in the oxygen tent and receiving oxygen through a nasal catheter. The abdomen was soft, and the liver and spleen were not palpable. Extremities were negative for any evidence of phlebitis.

Fourth Postpartum Day.—The patient was removed from the oxygen tent without return of cyanosis. She was not coughing or bringing up sputum. Temperature had been normal for two days.

Fifth Postpartum Day.—Chest x-ray showed that a comparison with the film of Jan. 30, 1947, revealed that the extensive areas of infiltration in both lung fields had completely resolved. This would indicate that the original pathologic process was pulmonary infarction. Approximately ninety-six hours had lapsed between films (Fig. 2).

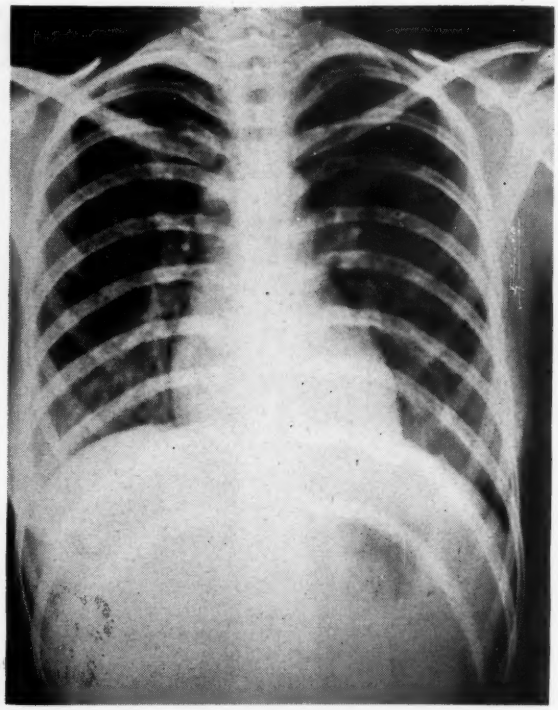

Fig. 2.—X-ray of chest ninety-six hours post partum.

The remainder of her hospitalization was marked by progressive improvement, and was complicated only by the development of an area of moderate pain in the left anterior axillary line at the costal margin. The latter was aggravated by deep inspiration, no cough, and gradually disappeared after three days. She was allowed out of bed on the eighth postpartum day, and was discharged on February 13, 1947, fifteen days after delivery, apparently fully recovered. She was followed up on two successive visits to the hospital at two- and six-week intervals; physical examination at these visits was completely negative, and she presented no complaints.

Discussion

It is to be noted at once that our case differs radically from those previously reported, since they were uniformly fatal. However, the existence of

sublethal and even subclinical forms of this condition was suggested by Steiner and Lushbaugh.[2] To quote: "It is impossible to state the true incidence of this condition at the present time because the sublethal and even subclinical forms which *undoubtedly exist* have not been recognized." They estimate the fatal incidence of this complication to be 1 in 8,000 obstetric cases from the material obtained from the Chicago Lying-in Hospital. Analysis of 72 obstetric deaths by Steiner and Lushbaugh showed that pulmonary embolism by amniotic fluid contents was the *most common cause of death* in the period during labor and within the first nine hours thereafter. "Instead of being considered a rarity among serious obstetric complications, this must be thought of as one of the commonest."[1]

The outstanding physical findings common to Steiner and Lushbaugh's cases and our own are: (1) cyanosis, (2) dyspnea, (3) fall in blood pressure, and (4) râles (pulmonary edema).

On the basis of their few cases, Steiner and Lushbaugh listed certain factors predisposing to this form of embolism. These included: (1) age: average age 32 years. (2) Parity: multiparas. (3) Tone of the uterus: tetanic or stronger than usual. (4) Character of the amniotic fluid: meconium or blood or excess of particulate matter. (5) Size of the fetus: exceptionally large. (6) State of the fetus: intrauterine fetal death in 50 per cent. Our case conformed to only one of these, i.e., the presence of a large amount of meconium in the amniotic fluid. The absence of strong or tetanic uterine contractions may have been substituted for by the strong suprafundic pressure made by the assistant during delivery. Yet this type of pulmonary embolism in the absence of labor contractions (occurring in a case of elective cesarean section) was demonstrated by Steiner and Lushbaugh in their second paper.[2]

Steiner and Lushbaugh discussed anaphylactoid shock as the probable cause of death in some of their cases.[1] This, combined with postpartum hemorrhage or pulmonary edema, was probably sufficient to cause the fatal outcome. In our case, uterine hemorrhage was clearly absent; anaphylactoid shock was not apparent; but pulmonary edema was striking. The absence of hemorrhage and anaphylaxis may have been largely responsible for her recovery. The fact that she was a young primigravida in good physical condition, and that she was not exhaused by a long, hard labor, may have been other factors favoring her recovery.

Steiner and Lushbaugh pointed out the experimental work of de Takats and associates[4] who showed that atropine reduces pulmonary vascular spasm by depressing reflexes initiated in the lungs which exert a depressant action on the heart, further embarrassing circulation through the lungs. In their own experiments they gave atropine to dogs before embolization by amniotic fluid-meconium mixture, which seemed to decrease the severity of the shock reaction if the embolizing dose was not too overwhelming. Fortunately, our patient received two doses of scopolamine (a member of the atropine series) for analgesia during the first stage, and also was given atropine at once upon recognition of the pulmonary edema. These apparently constituted another factor which led

to her recovery. Steiner,[5] in a personal communication, suggests that being under general anesthesia when embolization probably occurred may have abolished enough reflexes in the acute stage to tide her over.

Diagnosis

Since this condition has never been diagnosed before death and autopsy, there are no *clinical* criteria for its recognition in the living patient. In our case, the sudden profound shock could have been due to any one of several causes. However, the combination of dyspnea, cyanosis, and marked pulmonary edema without cardiac disease suggested a sudden pulmonary complication. Some form of embolism seemed to be the logical explanation, and that of amniotic material, while somewhat dramatic and unusual, was thought of in the absence of any other apparent cause.

Pulmonary edema was an almost constant finding in Steiner and Lushbaugh's series of autopsied patients, as well as in their experimental animals, including those animals which survived embolization and which were subsequently sacrificed for pathologic study. In this latter group they found it very difficult to identify particulate matter in the lungs seven days after embolization, and they concluded from this that the subsequent fate of this material is probably complete removal.

In view of this experimental work we believe that the diagnosis in our case is fortified by the roentgenologic evidence of almost complete clearing of the lung fields in approximately 96 hours.

The clinical picture in the absence of known previously existing heart or pulmonary disease, the roentgenologic findings, and clinical course, follow rather closely the diagnostic and experimental criteria suggested by Steiner and Lushbaugh.

Differential Diagnosis

We realize full well that in suggesting pulmonary embolism from amniotic fluid as the etiologic factor in this case we invite skepticism by some. Without definite microscopic evidence to prove our thesis this skepticism may be valid. Of the other likely diagnoses we shall consider and discuss the following:

1. *Postpartum hemorrhage:* Blood loss was estimated at 150 cubic centimeters. This cause can be immediately dismissed.

2. *Pulmonary embolism from vascular thrombi:* This was strongly entertained as evidenced by the therapy given, however, she had no known previous heart disease and none was demonstrated subsequently. The patient was closely examined and watched for the presence of thrombophlebitis in the pelvis and lower extremities, but this did not develop. The rapidity of clearing of the lungs as demonstrated by x-ray, the failure of more embolism to occur, and the rapid recovery of the patient, all seem to speak against the diagnosis of vascular embolism. Furthermore, embolism from vascular thrombi *usually* occurs later in the puerperium.

3. *"Eclampsia without convulsions":* In January, 1937, Teel, Reid, and Hertig[6] described a symptom complex of cardiac asthma associated with acute

pulmonary edema as a complication of nonconvulsive toxemia of pregnancy. As in our case, their patients were suddenly seized with severe dyspnea, cyanosis, orthopnea, and acute pulmonary edema, none of them having a known history of chronic hypertension, organic heart disease, or nephritis. But there the similarity ends. Teel, Reid, and Hertig's cases had definite toxemia—complete with hypertension, edema, albuminuria, and associated symptoms—our patient did not, her hypertension was transitory. None of their cases developed the profound state of shock with fall of blood pressure to 0/0 as did our case at the very onset of her attack. And, most convincingly—cardiac asthma with acute pulmonary edema would not explain the x-ray findings in the lungs of our patient.

4. *Aspiration of blood or stomach contents:* Our patient was anesthetized with unusual ease, did not vomit, or even cough during induction or in the course of the anesthesia, and, as far as is possible to ascertain, did not aspirate stomach contents or blood. Once again this diagnosis would not explain the roentgenologic evidence found in the lungs. Atelectasis would be the more likely x-ray picture.

5. *Nitrous-oxide asphyxia:* In asphyxia due to nitrous oxide there is a depression of the respiratory center (Cushny[7]) without apparent pathology in the lungs themselves. Usually the respiratory rate is decreased, and, if there is a rise in respiratory rate, it occurs in the initial stage of the asphyxia and is promptly followed by marked slowing of respiration. In our case the respiratory rate was greatly accelerated throughout. At this point it should be reemphasized that the gas-oxygen mixture contained a high percentage of oxygen according to the statement of the anesthetist, a member of the hospital professional anesthesia staff. The cyanosis which occurred intermittently during the delivery and repair seems best explained by the hypothesis that embolization, either by meconium or other particulate matter, occurred early in the course of delivery. Furthermore, if this had been a pure anesthetic phenomenon one would anticipate more rapid recovery. It is also impossible to explain the x-ray findings on an anesthetic basis.

Summary and Conclusions

1. We have presented the case of an 18-year-old primigravida who suddenly went into profound shock, developed acute pulmonary edema with cyanosis, and was in imminent danger of death immediately following the delivery of a living 6 pound 3 ounce frank breech.

2. The diagnosis of pulmonary embolic phenomena from particlate matter in amniotic fluid is suggested as the etiologic factor for the symptom complex which developed. We cannot didactically state that this is positively a case of amniotic particulate embolism, as there are no known means of making a positive clinical diagnosis in the living patient. However, we believe it presents the most likely explanation for the symptom complex that occurred. The literature contains no report of recovery of a patient from this syndrome.

3. The recovery of our patient may be explained by a series of fortuitous events: (a) early diagnosis and appropriate therapy; (b) excellent physical

condition of the patient; (c) the fact that she was under a general anesthetic during the embolizing episode; (d) the apparent rapid "absorption" or at least complete removal of the particulate matter from the lung fields as shown by x-ray.

4. The differential diagnoses admissible in this case were briefly discussed.

5. The case is presented to call attention to the possibility of recognizing this syndrome soon after its occurrence in order that proper therapy be started immediately to prevent a fatal termination.

6. The interdiction of intravenous fluids or the very slow administration of whole blood in the presence of acute pulmonary edema, atrophinization, morphine and oxygen are the important therapeutic measures. Withholding of intravenous fluids in the face of severe shock requires courage and exercise of clinical judgment.

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Addendum

Since this paper was submitted, three additional cases have been reported by P. Gross and E. F. Benz (*Surg., Gynec. & Obst.* **85**: 315-320, 1947).

ERYTHROBLASTOSIS FETALIS DUE TO INTRAGROUP Rh INCOMPATIBILITY

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IT IS well recognized that erythroblastosis fetalis is caused by isoimmunization of an Rh-negative mother by the Rh-positive cells of her fetus in 90 per cent of the cases.[1] In the remaining 10 per cent this syndrome is produced by Hr incompatibility,[2] or A-B-O intragroup incompatibility,[3-5] or by Rh subtype incompatibility where both mother and fetus are Rh positive but have different Rh phenotypes.[1, 6, 7] In the same manner by which an Rh-negative mother may become immunized by the Rh-positive cells of the fetus and develop Rh antibodies, an Rh-positive mother may form antibodies against the fetal Rh-positive cells which are of a different phenotype than her own. For example, a mother with Rh′ cells may have Rh_0 or Rh″ antibodies as the result of immunization by the Rh_0 or Rh″ cells of her fetus.

Since January, 1946, a special Rh clinic has been established at St. Catherine's Hospital. Every prenatal patient is tested for the Rh factor, and all Rh-negative mothers are referred to this clinic. Since the clinic has been fortunate in obtaining a supply of anti Rh′, anti Rh″ and anti Hr′ serums, as well as the standard anti Rh_0 serum, complete Rh typing is possible. Every Rh-negative mother with an Rh-positive husband is carefully studied and routine Rh-antibody determinations are made approximately every two weeks after the seventh month by both the agglutination and conglutination[8] techniques. In addition, with the cooperation of the Department of Pediatrics, every newborn baby is carefully observed for jaundice or other signs characteristic of the syndrome of erythroblastosis fetalis. Babies in whom such signs appear are thoroughly investigated for blood incompatibility due to Rh, intra Rh, Hr, or A-B-O incompatibility.

In the course of these studies, erythroblastosis fetalis was diagnosed in two Rh-positive infants born of Rh-positive mothers in whom the etiological factor was intragroup Rh incompatibility. Since only a few such cases have been recorded in the literature, these cases are reported.

CASE 1.—P. L., white, 28 years of age, gravida i, para 0, with a normal prenatal course, was delivered Feb. 21, 1947, of a full-term living female, weighing 6 pounds 10½ ounces, by breech extraction, after a thirty-eight-hour labor. Nothing abnormal was noted at birth. The baby's condition was satisfactory until the evening of the fourth day when icterus and listlessness were first observed. Blood count the following morning showed red blood cells, 3,640,000; hemoglobin 14.9 Gm., with 1 per cent normoblasts present. Although both mother and infant were Rh positive, a diagnosis of erythroblastosis fetalis was

made and the baby was given a transfusion of 100 c.c. of Group A Rh-negative blood. A similar transfusion was given on the sixth day. The baby responded well and the jaundice cleared in a few days. On discharge, on the thirteenth day, the red blood cell count was 6,090,000, hemoglobin 20 Gm., with no normoblasts noted. Weight was 6 pounds, 5 ounces, and the baby has continued to do well since. Blood studies of the baby, mother, and father are in Table I.

TABLE I

	BLOOD GROUP	ANTI Rh′ SERUM	ANTI Rh″ SERUM	ANTI Rh_0 SERUM	ANTI Hr′ SERUM	PHENOTYPE
Baby	A_2 MN	+	+	+	+	Rh_1 Rh_2
Mother	O MN	+	−	+	+	Rh_1
Father	A_2 N	+	+	+	+	Rh_1 Rh_2

The agglutination and blocking tests of the mother's serum for Rh antibodies were negative but the conglutination test was positive for Rh″ antibodies with a titer of 1 to 8. Group O Rh″ cells were used in all the antibody determinations. The maternal blood also had an anti A isoagglutinin titer of 1 to 2,048 and an anti B isoagglutinin titer of 1 to 8.

Comment: This is a case of erythroblastosis fetalis occurring in an infant born of an Rh-positive primigravida. Careful questioning of the mother elicited no history of previous transfusions or other blood therapy. Blood studies revealed a discrepancy between the Rh subtypes of the mother and infant. The mother lacked the Rh″ radical which the infant inherited from her father. Rh″ antibodies with a titer of 1 to 8 were demonstrated in the mother's serum by the conglutination technique. Although there were also present the requisites for A-B-O isoimmunization—mother group O, baby group A, with the mother's serum having an anti A isoagglutinin titer of 1 to 2,048—it is believed that the predominant etiological factor was the subtype Rh″ isoimmunization.

CASE 2.—B. W., white, 28 years of age, gravida ii, para i, delivered a seven months premature female spontaneously, Feb. 5, 1947. Delivery was complicated by a marginal placenta previa which was treated by simple rupture of the membranes and a transfusion of 750 c.c. of Rh-negative blood. The patient was originally considered Rh negative on the basis of a test by the standard anti Rh_0 serum. The infant was in good condition at birth, but was placed in an incubator on the usual premature regime. Her condition was satisfactory until the third day, when jaundice was observed. Blood count was red blood cells, 5,720,000; hemoglobin, 22 Gm. with 10 per cent normoblasts. A diagnosis of erythroblastosis fetalis was made and, since repeated blood counts showed no significant drop in red blood cells or hemoglobin, no transfusions were given. The jaundice persisted for eight days, gradually fading. The infant continued to thrive and gain weight. However, further blood counts showed: On March 22, six weeks after birth, red blood cells were 3,890,000, hemoglobin, 13.9 Gm.; on March 24, red blood cells were 3,730,000, hemoglobin, 12 Gm.; on March 31, red blood cells were 2,730,000, hemoglobin 9.9 Gm.; and on April 1, red blood cells were 2,530,000, hemoglobin, 9.2 Gm. At the age of eight weeks Rh-antibody study of the infant's serum disclosed the presence of Rh_0 antibodies with a titer of 1 to 128 by the agglutination technique and a titer of 1 to 16 by the conglutination technique. A transfusion of 80 c.c. of Rh-negative Group O blood was then given, and a similar transfusion of 85 c.c. two days later. During this time no clinical jaundice was noted, although the infant's icterus index was 25. The baby responded well to transfusion and continued to gain weight. Examination of the blood on April 7 revealed no antibodies. The baby was

discharged in excellent condition on April 12, weighing 5 pounds, 8 ounces, with red blood cells 5,900,000, hemoglobin 23.4 Gm., and has continued to do well.

Blood studies of the baby, mother, father, and brother are as follows:

TABLE II

	BLOOD GROUP	ANTI Rh′ SERUM	ANTI Rh″ SERUM	ANTI Rh_0 SERUM	ANTI Hr′ SERUM	PHENOTYPE
Baby	O	+	+	+	+	Rh_1 Rh_2
Mother	A	+	+	-	+	Rh′ Rh″
Father	O	+	+	+	+	Rh_1 Rh_2
First child	A	+	+	-	+	Rh′ Rh″

The agglutination and blocking tests of the mother's serum for Rh antibodies were negative but the conglutination test was positive for Rh_0 antibodies with a titer of 1:256. Group O Rh_0 cells were used in all the antibody determinations.

Comment: This case presents a classical picture of intra Rh incompatibility. The mother, although Rh positive, lacked the Rh_0 radical found in the baby's red cells. Her serum had anti Rh_0 antibodies with a titer of 1 to 256. Since the firstborn child had the same Rh phenotype as the mother, isoimmunization to the Rh_0 radical could not have occurred as the result of the first pregnancy. There was no history of previous transfusion to the mother. Consequently, the mechanism of isoimmunization in this case is similar to that occurring in a primigravida. An important finding in this case was the discovery of the Rh_0 antibodies in the baby eight weeks after birth. These antibodies were responsible for the progressive anemia. So far as we have been able to ascertain, this persistence of antibodies in the infant for so long a period of time has not been reported previously.[9]

Discussion

These two cases show that erythroblastosis fetalis does occur in infants born of Rh-positive mothers. Case 1 demonstrates that this syndrome may be present in the firstborn child. Obstetricians should be aware of this possibility, and family blood studies should be done in all cases of jaundice occurring in newborns. While it would be impractical to study prenatally Rh-positive mothers for antibody formation, nevertheless their babies should be observed for signs of erythroblastosis fetalis. In addition, Rh-negative primiparas with Rh-positive husbands should be examined for antibodies as carefully as Rh-negative multiparas. Complete reliance cannot be placed on a history of no previous blood therapy in primiparas, as it is entirely possible that blood may have been given to them early in infancy, unknown to themselves or their parents.

In Case 2, on the basis of testing with the standard 85 per cent anti Rh_0 serum, the mother would ordinarily be classified as Rh negative and the infant's erythroblastosis ascribed to the usual Rh incompatibility. Undoubtedly, study of such cases in the past with anti Rh′ and anti Rh″ serums would have disclosed other instances of intra Rh incompatibility. Since both of these serums are now available, more complete studies of the etiology of erythroblastosis fetalis can be made in the future.

The question of what kind of blood should be used in the therapy of these erythroblastotic infants and their mothers is of great importance. Blood of the

same Rh phenotype as the mother's would be ideal. Such blood, however, may be difficult to obtain. Since the serums of both infant and mother, although classified as Rh positive, contain Rh antibodies, it is more practical and easier to transfuse with Rh-negative blood than to obtain Rh-positive blood of the exact phenotype as the mother's. Thus, therapy for the infant should consist of Rh-negative blood, and, if transfusion is necessary for the mother, similar blood should be used. However, it is imperative that the Rh-negative blood used for transfusion in these cases should be classified as such on the basis of testing with the three Rh antiserums (anti Rh_0, anti Rh′ and anti R″) and not on the usual basis of testing with the standard anti Rh_0 serum. Serious complications may occur if this precaution is not observed. To illustrate, in Case 1, both mother's and infant's serum contained Rh″ antibodies. If blood classified as Rh negative after testing with the usual anti Rh_0 serum, but nevertheless containing Rh″ cells, had been given to the mother, a severe hemolytic transfusion reaction would have occurred. If the same blood had been given the infant, the erythroblastosis would have become more severe.

We believe it important to note that the same precaution should be observed in the designation of Rh-negative blood when transfusing cases of erythroblastosis due to true Rh incompatibility. The antibodies present in the serums of both mother and child may be Rh_0, Rh′ or Rh″ in type. The use of so-called Rh negative blood containing Rh′ or Rh″ cells might have serious consequences.

It is interesting to speculate on the reason for the persistence of antibodies for eight weeks after birth in the infant in Case 2. Perhaps the red cells of a premature infant absorb or react more slowly to antibodies. Perhaps the X protein postulated by Wiener[9] as necessary for the reaction of certain types of antibodies with red cells is insufficient or only weakly active in prematures. Certainly more study remains to be done on the period of time of persistence of antibodies in the newborn and the reason thereof.

The clinical course of these two cases which responded well to blood transfusions confirms the accepted opinion that erythroblastosis fetalis due to intra Rh incompatibility is less severe than when caused by true Rh incompatibility. This is due apparently to weaker antibodies. Two cases of erythroblastosis due to A-B-O incompatibility now being studied are also of a less serious nature. These observations will be reported subsequently.

Conclusions

1. Erythroblastosis fetalis does occur in infants born of Rh positive mothers, and also in infants born of primigravida.

2. Blood for transfusion of both mother and child, where erythroblastosis has occurred, must be classified as Rh negative on the basis of negative testing with anti Rh_0, anti Rh′ and anti Rh″ serums.

3. Rh antibodies have been found to persist in a titer of 1-256 in an erythroblastotic infant for as long as eight weeks after birth.

4. All newborn babies with jaundice should be investigated for blood incompatibilities.

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Addendum

Since this paper was submitted for publication, we have observed two additional cases of erythroblastosis in infants born of Rh-positive mothers. In one case, Rh_0 antibodies were found; in the other, Rh″ antibodies.

ERYTHROBLASTOSIS FETALIS IN THE INFANT OF A PRIMIGRAVIDA

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ALTHOUGH erythroblastosis fetalis in the firstborn is by no means unknown,[1] it is rare to find the condition, especially in the hydropic form, in the firstborn where there is no history of previous pregnancy or blood injection. Such a case is herein reported.

Levine and Waller[1] collected and reported nineteen mothers who had delivered their firstborn with erythroblastosis fetalis. These mothers had previously been transfused with blood without regard to the Rh factor. There is also presented, in the same paper, a group of nine cases of erythroblastosis fetalis in the firstborn of mothers not previously transfused. These infants were presumably Rh positive. In only one of these latter cases, however, was the blood of the mother positive for anti-Rh agglutinins, and the firstborn of this mother is listed as having erythroblastosis fetalis mild enough to need no treatment.

The case which I am reporting differs from those listed by Levine and Waller[1] in that: (1) There had been no previous pregnancies; the cervix was distinctly nulliparous. (2) Diligent questioning of the patient and the patient's family revealed not the slightest hint of blood by vein, or by injection subcutaneously, intramuscularly or intraperitoneally. (3) This patient showed anti-Rh_0 agglutinins in a dilution of 1:64, and (4) delivered a macerated, hydropic fetus.

Mrs. F. F. O. first came to the author's attention April 17, 1945, because of amenorrhea, frequency of urination, and enlargement of her breasts; her last menses began Dec. 3, 1944, and fetal movements had been felt one week prior to her initial visit. Her past, family, menstrual history, etc., were notable only for the absence of relevant positive data; she was one of five children all of whom were healthy. The patient's husband was in good health, 38 years old, weighed 165 to 170 pounds, and was 5 feet 11 inches tall.

Physical examination revealed that this 38-year-old primipara was 5 feet 2½ inches tall, weighed 143 pounds, had a blood pressure of 115/60, and a systolic mitral murmur. Her pelvic measurements were within normal limits, and nothing was found on bimanual examination except an intrauterine pregnancy of 18 weeks' duration. Laboratory work was negative save for a lowering of the hemoglobin to 13.5 Gm. (17 Gm. = 100%).

Because of the heart findings, a cardiologist was asked to see the patient. He reported a normal x-ray study of the chest, normal electrocardiogram, and added "we would be justified in not imposing any special restriction on account of the heart."

With the above in mind, the patient was treated as a normal expectant mother. Milk, vitamin D, and ferrous sulfate were prescribed, later to be replaced by medication containing dicalcium phosphate, viosterol, and ferrous sulfate. Urine, weight, and blood pressure remained normal as the pregnancy advanced, but in spite of iron therapy, a check on the patient's hemoglobin, June 19, 1945, showed the same level as the initial reading of 13.5 grams. When seen July 10, 1945, her blood pressure was 115/60, weight 152½ pounds, showing a gain in three months of 9½ pounds. In the next two weeks, however, the patient gained 5 pounds, and was placed on a dietary regime markedly restricting the calories.

On Aug. 1, 1945, five weeks before the expected date of confinement, a spontaneous rupture of the membranes occurred. This was followed in four hours by the onset of labor and admission to St. Luke's Hospital.

On admission, contractions of the uterus were occurring every two to three minutes and lasting thirty seconds. The fundus uteri (McDonald) measured 34 cm. Heart, lungs, blood pressure, temperature, pulse, and respiration were normal, but no fetal heart sounds were heard. One hour after admission to the hospital, rectal examination revealed the cervix 5 cm. dilated, with the vertex just below the ischial spines. Twenty minutes later the head was almost on the perineum with no cervix palpable. Forty-five minutes of second stage labor yielded no progress, and examination revealed the head to lie in a L.O.T. position with antepartum fetal death. This had been suspected by the absence of fetal heart sounds, and was confirmed by finding maceration of the scalp. The head was manually rotated with ease to an anterior occiput, and an easy low forceps served to complete delivery of the head. Moderate difficulty was experienced in the extraction of the shoulders and abdomen. The diagnosis of fetal hydrops seemed obvious. Weight of the baby was 9 pounds 2 ounces.

At the time this patient was under observation, it was the author's practice to secure Rh determinations only on multiparas who had had previous stillbirths or neonatal deaths. Blood was drawn immediately after the delivery and reported Rh negative, blood group A, and the husband blood group B, Rh positive. Dr. Levine further reported the blood of the patient as follows: "The blood shows strong anti-Rh_0 agglutinins in a dilution of 1:64; Group A, Rh^1, Hr. positive." The patient later donated 500 c.c., of blood, the anti-Rh_0 serum from which was used successfully for Rh typing.

Intrapartum and postpartum blood loss was minimal, and it was not necessary to transfuse the patient. On the sixth postpartum day the hemoglobin was 70 per cent Sahli, with 3,710,000 red blood count. Ferrous sulfate was depended upon to correct this slight anemia. There were no complications, and the patient was discharged in good condition. At the six-week check-up the hemoglobin had risen to 90 per cent Sahli.

Essential findings in the pathologic examination of the baby and placenta were as follows:

The baby was a term female with markedly distended abdomen over which the skin was thick, edematous, and macerated. The peritoneal, pleural, and pericardial cavities were filled with bloody fluid. The liver and spleen were considerably enlarged, but microscopic examination was not informative because of marked autolysis. However, near the capsule of the liver, numerous normoblasts were to be seen. The other organs were essentially normal.

The placenta measured 28 by 19 by 4 cm., and was firm, yellowish-white, and meaty. Microscopically, the cuboidal cells lining the villi were young in appearance, and the villi contained large pale young cells characteristic of the placenta of erythroblastosis. Anatomical diagnosis was erythroblastosis fetalis with hydrops.

Summary and Conclusions

1. Severe erythroblastosis fetalis (fetal hydrops) can occur in primigravidas who have not previously received blood in any manner.

2. Rh determinations should be made on all pregnant women, and Rh antibody studies made on all pregnant Rh-negative women in the latter weeks of gestation.

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TRAVEL IN PREGNANCY

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OBSTETRICIANS are not in complete agreement as to how much the pregnant woman may travel without danger to the pregnancy. The practice of our departmental staff is to permit travel by plane, Pullman, or ocean steamer up to the thirty-fourth week. However, before any long trip is made the patient is examined vaginally to determine the condition of the cervix. Travel by automobile is permitted up to a maximum of 300 miles per day with an adequate rest period of at least two hours at the end of 150 miles. With these restrictions long automobile trips are permitted. If the patient has shown any evidence of a threatened abortion or has a history of abortion or premature labors, travel by any means is restricted or forbidden. During the war there was so much travel by pregnant women that it became obvious that the instructions were too restricting. It was, therefore, deemed advisable to gather further information on this subject of travel in pregnancy.

Diddle, in September, 1944, published a paper on this subject. His data were collected on obstetric dependents of armed forces personnel. He was located on an island 127 miles from the mainland and connected by a rough asphalt and coral highway. The nearest railway was 170 miles away on the mainland. In order to commute from the island to the mainland the patients had to travel over this highway by car or bus. In his series, of 289 women who traveled before the fourth month, 16, or 5.6 per cent, aborted or threatened to abort; whereas 17.9 per cent of the nontravelers aborted or threatened to abort. Only one patient of his seemed to abort from travel in itself. This was the case of a woman who had taken a motorcycle ride a few hours previously. His conclusions were that neither the distances covered, nor the method of travel, nor the time of month a journey was undertaken revealed any significant differences in the incidence of abortion.

In the Chicago Lying-in Hospital over a period of approximately two and one-half months, 681 patients were interviewed a few days following delivery. They were asked for the following information: (1) whether they had traveled at any time during their pregnancy, (2) where they traveled, (3) date of their trip, (4) method of travel, and (5) discomfort or illness during or immediately following the trip.

This group of 681 patients can be divided into the following groups:

1. no travel in present pregnancy		337
2. traveled in present pregnancy		309
3. abortion with no travel preceding		18
4. abortion with travel preceding		17
	total	681

These patients were also asked regarding previous pregnancies in which they had traveled and in a few instances concerning previous abortions. These additional pregnancies bring the total to 719 pregnancies studied.

These 719 pregnancies can be divided into the following groups:

1. no travel		337
2. traveled during pregnancy		341
3. abortion with no travel preceding		24
4. abortion with travel preceding		17
	total	719

An abortion is considered in this survey as any termination of pregnancies prior to twenty-eight weeks. As to the criteria as to whether a patient traveled, a patient is placed in the no travel category in this survey unless the trip was 100 miles or farther. There are a few exceptions to this in the case of some patients who made numerous trips of short distances. They will be discussed individually later in this report. In the case of abortions any trip other than ordinary short rides around the city places the patient in the traveled category regardless of whether the trip was 100 miles or not.

It is acknowledged that there are many limitations in this survey, limitations which are unavoidable because of their complexity. Among these limitations which influence the accuracy of this report are the type of roads over which the patient traveled, and if the trips were made by going for long hours at a time without rest stops, and many other factors which are difficult to record statistically. The first portion of this survey will be devoted to the non-abortive cases, and the second portion to the abortions.

Table I gives the percentage of total number of pregnancies with traveling in each lunar month by various methods. The peak of traveling was reached in the seventh month. The greatest part of the traveling was done by automobile and train, with very little by bus.

As to the distances traveled by these women there was no large concentration of a group of women having traveled a short distance or a long distance. There is one exception to this in the distances traveled by automobile in the 100 to 199 mile category for all months and in the 100 to 299 mile category for the sixth through the ninth months. In this instance there is a large group of women having traveled less than 300 miles. Other than this the distances traveled by these women are spread rather evenly from 100 miles to over 3,000 miles.

As to plane travel, most of the distances traveled are large as is to be expected, due to the inability to take short plane trips on most airlines.

Bus travel was used mainly for short trips, very few patients taking long trips by this method.

Of the boat trips, there were only three—one each in the fourth, fifth, and sixth lunar months. The trip in the fourth lunar month was an ocean voyage from England to New York. The other two boat trips were Great Lakes vacation cruises.

Several of the patients traveled a good deal throughout their pregnancies with no apparent ill effects.

Patient K. M., No. 390168, traveled by train from New York to Boston in the sixth month; from Boston to Los Angeles in the seventh month; from Los Angeles to San Francisco in the ninth month; and from San Francisco to Chicago in the tenth month.

Patient A. T., No. 381713, lives in Champaign, Ill. She traveled by train to Chicago and return (276 miles round trip) every three weeks for her clinic visits from the fifth month to the time of delivery.

Patient L. C., No. 378751, traveled by car 150 miles every weekend during her pregnancy.

Patient A. K., No. 375491, traveled by car between Chicago and St. Louis, Mo. (600 miles round trip) every three weeks during her second, third, fourth, fifth, sixth, and seventh months.

TABLE I

MONTHS GESTATION	PERCENTAGE OF TOTAL PREGNANCIES WITH TRAVELING	TYPE OF TARVEL
1	3%	car
	1.6%	train
2	3.6%	car
	2.2%	train
	0.2%	plane
	0.1%	bus
3	3.6%	car
	3.6%	train
	0.8%	plane
	0.1%	bus
4	5.5%	car
	4.8%	train
	0.8%	plane
	0.2%	bus
	0.1%	boat
5	5.0%	car
	5.0%	train
	1.3%	plane
	0.1%	bus
	0.1%	boat
6	7.0%	car
	5.0%	train
	1 2%	plane
	1.1%	bus
	0.1%	boat
7	9.3%	car
	6.1%	train
	0.9%	plane
	0.7%	bus
8	9.1%	car
	4.5%	train
	0.7%	plane
	0.7%	bus
9	6.9%	car
	2.5%	train
	0.4%	plane
	0.1%	bus
10	2 0%	car
	1.2%	train
	0.1%	plane

Patient M. H., No. 388642, in her first pregnancy traveled by train from Washington, D. C. to Chicago (700 miles) in the first month; from Chicago to Miami (1,391 miles) by train in the third month; from Miami to Washington, D. C. (1,117 miles) by train in the third month;; from Washington, D. C. to Norfolk, Va. (175 miles) by automobile in the fourth month; from Norfolk, Va., to Washington, D. C. to Chicago (875 miles) in the fifth month by train; and from Chicago to Miami (1,391 miles) by train in her eighth month.

Patient C. B., No. 380263, made five plane trips between Chicago and Kansas City (1,500 miles round trip) during the third, fourth, and fifth months.

There are many other patients who traveled extensively during their pregnancy, and those listed above are but a few examples.

Attention can now be given to the various methods of travel. In general, patients found that, when traveling by car, short hours of driving with frequent rest stops left them feeling much less fatigued than when driving continuously for several hours.

In traveling by train, streamliners and Pullman accommodations were much preferred; the patients traveling by coach becoming fatigued, nauseated etc., much more readily. Those that traveled by bus did not find it as comfortable as traveling by Pullman or private car.

Those patients traveling by plane preferred that method, especially those who had also traveled by other methods during their pregnancy. There were a few cases of nausea and vomiting, but these occurred when the plane trip was made in bad weather.

Abortions

As regards the abortions, 24 occurred in women giving no history of having traveled at any time during their pregnancies. In addition, ten of the patients who went to term had spotting during their early months but had done no traveling up to the time of the spotting. This makes a total of 34 abortions and threatened abortions who give no history of travel.

Seventeen patients gave a history of having traveled at some time prior to their abortion. In addition, two patients who went to term had spotted in early pregnancy immediately following a trip—one after a 600 mile train trip in her fifth month; the other following a short automobile ride over a very rough road in her third month. This gives a total of 19 abortions and threatened abortions in whom a history of traveling is given.

In condensed form:

1. patients with no travel	34	64.2%
2. patients with a history of travel	19	35.8%
total	53	100.0%

Of the 19 cases of abortions and threatened abortions in women who traveled, only eight had traveled at any time near enough to the onset of symptoms for the traveling to have been a possible factor. In four of these cases the onset of symptoms immediately followed the trip, and of these four patients, two went on to a full-term pregnancy.

Therefore, there are two cases which actually aborted and in whom the onset of symptoms was immediately preceded by a trip. Whether or not these patients, or the others for that matter, would have aborted if they had not traveled is impossible to say. In four cases, however, it seems definite that the trip was the immediate precipitating factor of symptoms even though other factors may have been involved.

Conclusions

In 339 pregnancies traveling was done without any threat of abortion. In two additional cases threatened abortions were probably the result of a trip, but the pregnancies went on to term.

In 17 abortions with a history of traveling, only six had traveled near enough to the time of onset of symptoms to be a possible factor.

Hence, of all 358 patients who traveled, in eight or 2.2 per cent, could the trip have been a factor in threatening or producing abortion, and in four, or 1.1 per cent could the trip be said to be the immediate precipitating factor. Of this latter group of four, two, or 0.6 per cent, actually aborted, the other two going on to term.

From the extent of traveling done by pregnant women in all stages of their pregnancies without complications, it would appear that traveling is not harmful to the majority.

Reference

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LOW MATERNAL MORTALITY WITH PERSISTENCE OF HEMORRHAGE AS THE CHIEF CAUSE OF DEATH; AN ANALYSIS OF PUERPERAL DEATHS IN BROOKLYN DURING 1946*

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THE importance of a program for the prevention of mortality in childbirth can be best shown by comparison of the maternal death rate of Brooklyn for 1946 with the rate for 1937, the year the Brooklyn Committee on Maternal Welfare began its analysis of maternal deaths.

In 1937 there were 164 puerperal deaths in Brooklyn, and the maternal death rate was 40.7 per 10,000 live births. In 1946 this rate had fallen to 8.7, and there were but 57 puerperal deaths. It would appear that if the maternal death rate of 1937 had not been reduced, 187 more women in Brooklyn would have died of childbirth in 1946 alone.

A reduction of 80 per cent is notable, even though maternal death rates are declining generally. The latest figure available for the United States (1944) is 23 per 10,000 live births. The puerperal mortality rate for the entire City of New York in 1946 was 10.4 per 10,000 reported terminated pregnancies. This figure for 165,716 total births in this city of nearly eight million people is extraordinarily good. The rate for Brooklyn has been the lowest of the five counties included in New York City for the past three years (Fig. 1).

Our Brooklyn experience is of more than local importance. Our critical analyses of the causes of maternal mortality do not depend solely upon the factual data of certificates of death. The case records in our files vary in quality, and data essential to a good case report are often lacking, yet the controllable factors of death are usually found. It may be said with confidence that deductions made from statistical tabulations based upon the meager information on the certificate of death can never be more than generalized.

More births occur in Brooklyn than in more than half of the individual states. More babies are born in Brooklyn than in any other borough of the City of New York, more than in Philadelphia, and nearly three times as many as in Boston. There are few states comparable to the City of New York, and but few cities of the United States comparable to Brooklyn alone. (Table I.)

In 1946, fifty-seven deaths in Brooklyn were assigned to puerperal causes by the Bureau of Records and Statistics of the Department of Health of the City of New York. The causes of death are listed in Table II, and comparison is made with the two previous years.

Nonwhite Deaths[8]

The nonwhite population of New York City is an important statistical factor, since the puerperal death rate of Negro women in 1946 was two and one-half times that of white women, while their death rate from abortion was more than ten times as great. In Brooklyn the puerperal mortality rate for Negro women was nearly twice as high as the white, and their abortion mortality

*Read at a meeting of the Brooklyn Gynecological Society, May 2, 1947.

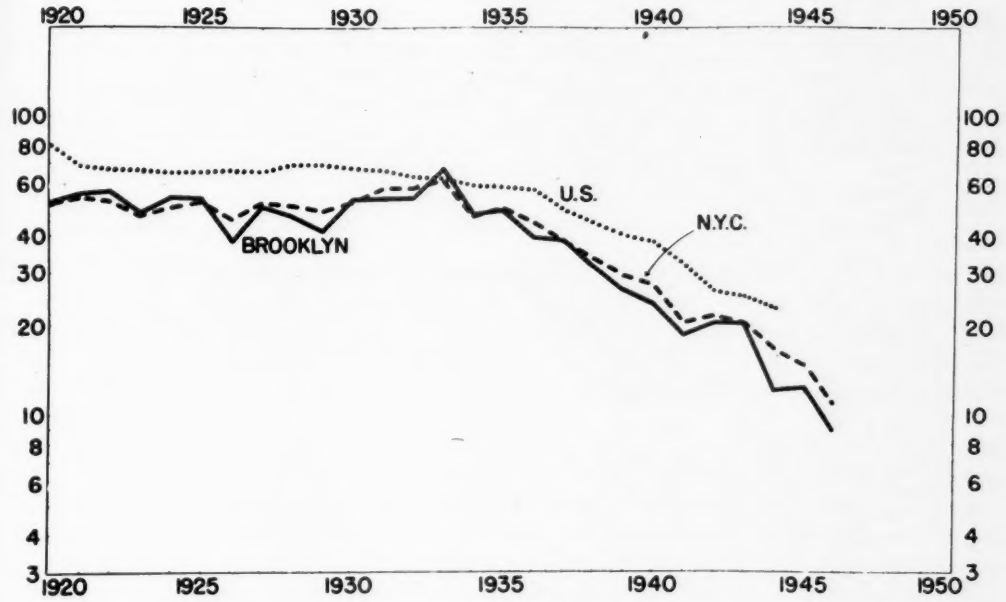

Chart 1.—Puerperal mortality of United States, rate per 10,000 live births; city of New York, rates per 10,000 total births; and Brooklyn, rates per 10,000 total births.

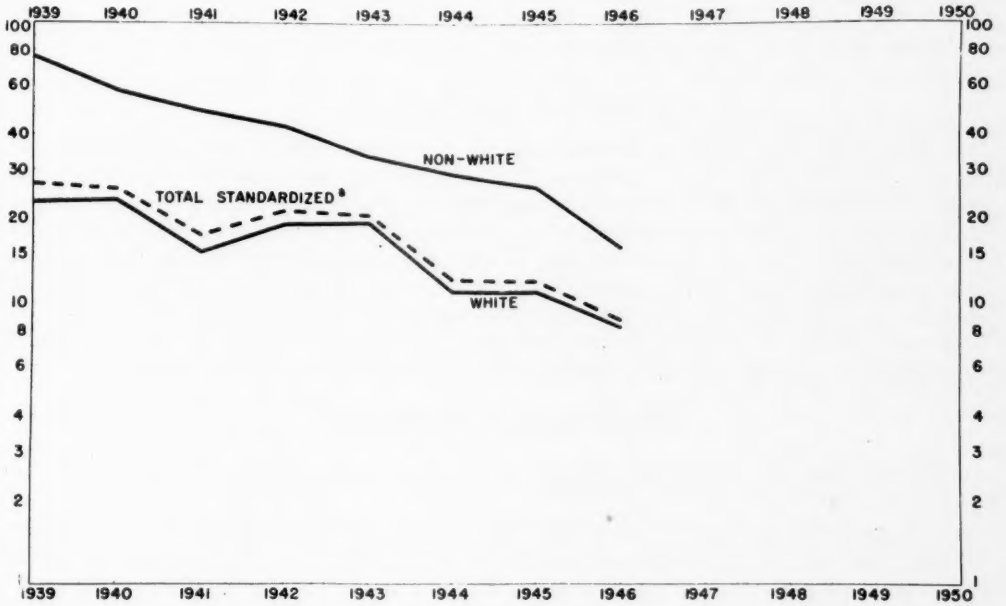

Chart 2.—Borough of Brooklyn puerperal mortality, rates per 10,000 total births—according to color.

*Corrected for color—Distribution of New York City population according to color, 1940 census.

TABLE I. STATISTICAL IMPORTANCE, NEW YORK CITY AND BROOKLYN, 1944
LIVE BIRTHS (IN THOUSANDS) BY PLACE OF OCCURRENCE

NEW YORK CITY	122	BROOKLYN	44
STATES		CITIES	
New York	229	Los Angeles	66
Pennsylvania	178	Chicago	59
California	177	Philadelphia	38
Texas	164	Detroit	35
Illinois	139	Boston	18
Ohio	132		

TABLE II. MATERNAL DEATHS (BROOKLYN, 1946)

CAUSE		1946	1945	1944
Abortion	140-141	7	11	10
Ectopic	142	2	2	3
Hemorrhage	134-146	8	13	8
Toxemia	144-148	12	5	11
Infection	147	12	17	20
Accidents of labor	149	11	10	8
Other	145-150	5	9	2
Total		57	67	62
Total births		64,559	54,293	51,082
Rate		8.7	12	12.2

rate eight and one-half times as high as that of white women. The puerperal mortality rates for all boroughs are corrected for color according to the 1940 census population. All New York puerperal mortality rates are calculated from the number of reported terminated pregnancies. This is done nowhere else in the United States. Whether this statistical method is better than the usual live birth ratio, is, in my opinion, doubtful (Fig. 2).

Nonpuerperal Deaths[15]

It is common practice, in analysis of deaths associated with childbirth, to pay no attention whatever to those not assigned by the statistician directly to puerperal causes, since no matter what they include or how many there are they do not affect the maternal death rate. No good program can be planned, however, without study of these deaths, if only because a large number of deaths due to cardiac disease will not otherwise be found. The total number of deaths associated with childbirth, but officially assigned to nonpuerperal causes, in 1946 was fifteen. Two suicides are included, one after cesarean section, the other during labor. In nine cases death was due to Rheumatic heart disease.

Deaths Early in Pregnancy

Death was due to ectopic pregnancy in two cases, and seven cases were assigned to abortion.

In the ectopic cases, death was due to failure of diagnosis in both cases. In one case in which diagnosis had been missed by two physicians, the third found the patient dead in bed at home. In the other case death followed laparotomy, after curettage in another hospital.

In four cases abortion had been induced, with perforation of the uterus and intestinal injury in two cases; in two others in which hemorrhage was profuse for several hours, death was finally due to infection. Included is a case of eclampsia in the twenty-seventh week, in which labor was induced by manual dilatation and bougie after several convulsions and fetal death.

Toxemia

Officially assigned to toxemia were twelve cases; three more were found in the infection group, and one in the abortion group. Prenatal care was inadequate in all but two cases. One patient with eclampsia was but 15 years of age. In three cases hemorrhage was said to have been considerable, though death was due to eclampsia. Convulsions occurred in nine cases. Cesarean section was performed five times, in two cases after convulsions.

Infection

Included in this group of twelve cases are three deaths due to cardiac disease, since death had been attributed to pulmonary embolism. Altogether, embolism was mentioned in ten of the twelve cases assigned to infection. A case of eclampsia is included, and three cases of death shortly after delivery in which dyspnea, paroxysmal cough, and cyanosis point to anesthesia as the cause.

The statistical rule which, since 1940, has assigned embolism to infection as a cause of death unduly weights this figure. Sudden death shortly after delivery is more often due to a cause other than embolism. Statistics may show that there has been no statistically significant decrease in the puerperal septicemia rate of the City of New York, and that improvement has been effected to a large extent by a decrease in deaths from all causes other than infection. Our opinion is otherwise.

In but one case of embolism was this diagnosis proved by autopsy. In one case in which death occurred under anesthesia within half an hour of delivery, cerebral embolism was said to be the cause. In two cases, clinical embolism occurred on the third and fifth days in women who were up and about.

Hemorrhage

Formally assigned to hemorrhage were but eight deaths. In two of the three cases of postpartum hemorrhage, hysterectomy was performed after other measures had failed. Hemorrhage was the actual cause of death, however, in six cases otherwise tabulated as abruptio placentae,[2] rupture of the uterus,[3] and probable rupture of the uterus.[1] As much as eight units of plasma were given to one patient before blood was procured just prior to hysterectomy. In another case of postpartum hemorrhage bleeding continued for three hours in bed, while four units of plasma were administered; the uterus was continuously massaged, but not explored.

Hemorrhage was the actual cause of death in 35 per cent of the fifty-seven puerperal deaths. The following table will indicate the rubrics in which deaths due to hemorrhage were found (Table III).

TABLE III. HEMORRHAGE AS THE CAUSE OF MATERNAL DEATH (BROOKLYN, 1946)

	OFFICIAL STATISTICS	HEMORRHAGE DEATHS
Abortion	7	4
Ectopic	2	2
Hemorrhage	8	8
Toxemia	12	1
Infection	12	-
Accidents	11	3
Other	5	2
Total	57	20

Cesarean Section

Cesarean section was associated with death in seventeen of the total number of seventy-two deaths, or in fourteen of the fifty-seven deaths assigned to puerperal causes. It is curious that death was due to infection in but three cases. In three cases in the nonpuerperal group death was due to Addison's disease, suicide, and cardiac disease; and in the puerperal group to eclampsia (one), uremia (one), aspiration asphyxia (one), atelectasis (two), cardiac disease (two), transfusion (two), spinal anesthesia (one), and infection (three). All three deaths from infection followed the lower segment operation, two after long labor; in the other case death on the eleventh day followed operation upon a patient whose hemoglobin was 40 per cent; 500 c.c. of plasma were administered just prior to operation, and 500 c.c. of blood immediately afterward; at autopsy thrombosis of the left common iliac vein and pulmonary embolism were found.

Anesthesia

It is not possible to learn the true importance of anesthesia from statistics of maternal death. Even though death is stated to have been directly due to aspiration of vomitus, anesthesia is not tabulated as a cause of death. Only from case records can the frequency of death from anesthesia be discovered. Its importance is not widely appreciated.

Anesthesia was an important cause of death in Brooklyn in 1946. Deaths may be readily separated into three groups as due to the toxic action of the anesthetic drug, to aspiration asphyxia, and to atelectasis, whether from aspiration or not. These deaths are of so great importance that the essential data of each case are reported.

Case 1.—Age 18 years, cardiac, in labor four hours at term. Classical cesarean section under spinal anesthesia. Sudden death occurred with delivery of the child, twelve minutes after administration of 50 mg. of procaine.

Four deaths were due to aspiration asphyxia.

Case 2.—Age 27 years. Extraperitoneal cesarean section under gas, oxygen, ether sequence after fifty hours of labor. At completion of the operation, vomiting occurred. Labored breathing and deep cyanosis followed. Death occurred during laryngeal suction.

Case 3.—Age 41 years. Under gas, oxygen, ether anesthesia hysterectomy for rupture of the uterus had been nearly completed when vomiting occurred. Anesthesia was forced at this point and sudden death followed, despite removal of a large amount of material from the trachea and bronchi through a bronchoscope.

Case 4.—Age 27 years. Low forceps delivery under gas, oxygen, ether sequence after seven hours of labor. Vomiting occurred during repair of episiotomy. Dyspnea and cyanosis followed. Death occurred twenty-four hours later with a temperature of 103° F., pulse 145, and respiration 48. X-ray showed "massive bilateral pneumonia."

Case 5.—Age 32 years. Breech extraction under open ether anesthesia. As soon as anesthesia was discontinued cyanosis deepened rapidly, bloody froth appeared at the mouth, and death occurred in twenty minutes.

Atelectasis follows bronchial obstruction or decreased ventilation of the lung field. Mucus is aspirated more often than vomitus, yet aspiration is not essential. There were three cases in which the atelectasis syndrome appears to be typical. Essential data follow:

CASE 6.—Age 38 years. Classical cesarean section under spinal anesthesia supplemented by nitrous oxide and ether. Great apprehension in the operating room and afterward. Fairly well for a few days except for moderate fever, pulse acceleration, and fear of impending death. On the sixth day her temperature was 104° F., pulse 140, and signs of consolidation were found in the lower lobe of the right lung.

CASE 7.—Age 36 years. Lower segment cesarean section under fractional spinal anesthesia was performed after thirty-six hours of labor. The patient was coughing a great deal the next day, when coarse râles were present over both lung fields, and diffuse opacity of the left lung base was reported by x-ray. Death on the sixth day with stertorous breathing, deepening cyanosis and very rapid pulse.

CASE 8.—Age 36 years. Lower segment cesarean section under gas, oxygen, ether sequence after thirty hours of labor. The next day fever was 102° F., pulse 144, and respirations 36. Cough was frequent and paroxysmal. Death on the following day was ascribed to pneumonia.

From 1937 to 1946, inclusive, fifty-one deaths from anesthesia have occurred in Brooklyn. Detailed report of forty-three cases prior to 1946 has been accepted for publication.[1]

Rheumatic Heart Disease

Cardiac disease is of great importance. There were fourteen deaths due to this cause; nine were assigned directly to cardiac disease, and so not tabulated as maternal deaths; five were assigned to puerperal causes. Prenatal care was inadequate in all but two cases. In three cases cesarean section was performed—in one case just before death in a futile attempt to save the child, and in two cases under spinal anesthesia, which, it is likely, is contraindicated in cardiac disease. For brevity the essential data are set down in Table IV. The important deduction to be made is that hospitalization should be immediate and continue until term, once failure has occurred.

TABLE IV. DEATHS DUE TO RHEUMATIC HEART DISEASE ASSOCIATED WITH CHILDBIRTH, BROOKLYN, 1946

STATISTICAL ASSIGNMENT	DURATION OF PREGNANCY	DELIVERY	SIGNIFICANT DATA
Nonpuerperal	6 months	Not delivered	Admitted in failure, death 3 days
Nonpuerperal	6 months	Not delivered	Admitted in failure, death 4 hours
Nonpuerperal	4 months	Not delivered	Died at home, failure previous delivery
Nonpuerperal	8 months	Not delivered	Admitted in failure; death 1 day
Nonpuerperal	36 weeks	Not delivered	Died at home; failure 2 months
Nonpuerperal	Term	Not delivered	Admitted in labor; death 10 hours
Nonpuerperal	Term	Not delivered	Admitted in labor; death 5 hours
Nonpuerperal	Term	Forceps	No anesthesia, long labor, death 12 hours later
Nonpuerperal	28 weeks	Cesarean section	Decompensated; spinal, death 5 days
Infection	32 weeks	Spontaneous	Short labor; no anesthesia, death 4 hours later
Infection	Term	Spontaneous	Short labor; no anesthesia, death 1 hour later
Infection	32 weeks	Cesarean section	Decompensation; antemortem; local
Accidents	40 weeks	Forceps	Admitted in failure, death 8 hours later
Accidents	Term	Cesarean section	Never decompensated; spinal

Comment

It is quite a problem to present in manageable form the tremendous amount of material available to us. It is difficult to make numbers interesting. They

are but a means to an end. Actually, our purpose is to examine intensively obstetric experience in a large city. That this can be done in no way other than by review of case reports is clear. Our maternal death rate is at a new low level, yet the principal controllable factors are associated with the trauma of delivery.

We need more than case records of death. We need also an analysis of the nature of our lying-in institutions and better knowledge of their obstetric practice. It is not unjust to say that all too often plasma is held to be a satisfactory substitute for blood, and that adequate blood reserves are not maintained at all of our hospitals. Hemorrhage is still the principal cause of maternal death in Brooklyn. The red river is known to run through our city, yet its course and its tributaries elsewhere in the United States have not yet been charted.

During the last ten years, eighteen maternal deaths have been due to aspiration of vomitus during administration of anesthesia for delivery or shortly afterward. The number of aspiration asphyxia deaths for 1946 represents a new high for any one year. The danger of aspiration is not fully appreciated by many who practice obstetrics, and even the well-trained anesthetist may be unaware that the obstetric delivery, whether abdominal or pelvic, is not comparable to the elective surgery of the operating room. Repressed intrapartum fears often make induction troublesome, since self-control is abolished in this stage; and if induction is not smooth, the entire period of anesthesia may be stormy. Varying depth of anesthesia because of anxiety for the welfare of the baby, or significant delay just before induction is complete are equally dangerous.

The purpose of prenatal care is safe delivery; it is a waste of time if the danger signals set by pre-eclampsia and rheumatic heart disease are ignored. In either case, no matter when significant symptoms appear, there is no substitute for continuous hospitalization. And in either case, election of cesarean section as the method of delivery is not often wise.

For the last ten years approximately one-third of our maternal deaths, exclusive of those early in pregnancy, have been associated with cesarean section. Not only do its indications need close examination but a high standard of performance is required, with attention to every detail.

But safe conduct through any delivery requires no less of the obstetrician. Obstetric skill is not acquired without concern for every detail. No matter how simple, no two deliveries are just alike, even though spontaneous. Everyone who practices obstetrics must be aware of its hazards and make a studied effort to reduce or eliminate the number of deaths which might be called avoidable. By its very nature obstetrics is a sacred discipline.

Grateful acknowledgment is made to the Visiting Nurse Association of Brooklyn for invaluable clerical help.

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32 Remsen Street

A PRELIMINARY REPORT ON THE CLINICAL USE OF METHERGINE

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THE intravenous use of oxytocic drugs has proved of great value in preventing and reducing obstetric hemorrhage. The present study was therefore undertaken in order to determine the effectiveness of Methergine, a synthetic ergonovine derivative. This substance was partially synthesized by Stoll and Hofmann, and subsequently studied pharmacologically by Kirchhof and his associates.

Previous clinical studies by Tollefson, Cartwright, and Rogers, Roberts, Hepp, and Evans, and Tritsch and Schneider have demonstrated Methergine to be a potent oxytocic as regards reduction of blood loss, shortening of the third stage of labor, and promotion of involution.

My objective in using this new synthetic drug, Methergine, was to observe its action on the postpartum uterus; the duration of the third stage; the amount of blood loss; postpartum pain; the character and amount of lochia; and finally to compare the amount of the drug necessary to obtain the same results as have been obtained with other oxytocics.

Procedure

In all of the 180 cases in this series, a 1 c.c. ampule of Methergine, containing 0.2 mg. of the drug, was given intravenously immediately after the birth of the child, and another 1 c.c. was given intramuscularly as soon as the placenta was delivered. Following the first intravenous injection, the uterus was massaged in order to attempt the expression of the placenta with the first hard contraction. This technique of manual expression, in my opinion, minimizes the blood loss and also the incidence of incarcerated placenta.

Following delivery, the first Methergine tablet (0.25 mg.) was given orally in about four to six hours, and repeated three times daily for two days unless more was thought necessary due to excessive bleeding. The latter was the exception rather than the rule.

From the birth of the child to the time when the patient was taken down from the stirrups, all the blood lost vaginally, including that from the episiotomy, was collected in a sterile basin, held below the buttocks, and measured.

Duration of the Third Stage

A short third stage was characteristic of this series. As a rule, the first contraction after the intravenous use of Methergine was exceptionally forceful. After expression of the placenta, the uterus became very hard and round, maintained this tone for several hours, and could be palpated more often in the midline than to one side. By the time the patient's legs were off the stirrups, there was usually only a slight trickle of blood from the vagina and, if the fundus of the uterus was held abdominally between the palms of both hands for fifteen to twenty minutes, this status quo lasted until the action of Methergine had worn off hours later.

The shortest third stage was one minute, with one exception, when the placenta was expressed with a stillborn fetus. The longest duration was forty-one minutes, giving a mean average of four and one-half minutes. The average length of the third stage in primiparas was 3.2 minutes, and in multiparas 4.6 minutes.

The length of the third stage in 157 cases (87.2 per cent) was up to five minutes. In 18 cases (10.0 per cent), it was between six to fifteen minutes, and in five cases (2.8 per cent) it was between sixteen to forty-one minutes.

TABLE I

CASES	MINUTES	PERCENTAGE
157	0 to 5	87.2
18	6 to 15	10.0
5	16 to 41	2.8

Blood Loss in Third Stage

It is interesting to note that one-half of this series fell into the group where the blood loss ranged between 50 to 100 c.c. There were 90 cases, of which 40 were primiparas and 50 multiparas.

The next largest group numbered 56 patients (16 were primiparas and 40 multiparas) who lost up to 50 c.c. of blood. The third group of 27 patients (17 primiparas and 10 multiparas) lost between 110 to 450 c.c. of blood. The fourth group numbered seven, who lost over 450 c.c., and all of these were multiparas; two lost 450 c.c., four lost 500 c.c., and one lost 800 c.c.

TABLE II

AMOUNT C.C.	PRIMIPARAS		MULTIPARAS	
	NO.	PER CENT	NO.	PER CENT
0 to 50	16	21.9	40	37.4
60 to 100	40	54.8	50	46.8
101 to 449	17	23.3	10	9.3
450 and over	0	0.0	7	6.5
Totals	73	100.0	107	100.0

A brief review of three cases who lost more than 50 c.c. and less than 450 c.c. is presented:

CASE No. 21.—R. A., aged 26 years, para i. Pressure on admission 200/100, postpartum 76/66. Eclampsia with abruptio. Outlet forceps and episiotomy. Morbidity 99.2 to 100.0. Postpartum shock. Uterus five fingers above symphysis immediately post partum, and one fingerbreadth above symphysis on discharge. Placenta delivered with stillborn. Scant serous lochia throughout. No abdominal pain throughout. Measured blood loss third stage 200 c.c. The complicating toxemia and premature detachment of the placenta were, no doubt, responsible for the greater blood loss.

CASE No. 64.—C. B., aged 24 years, para i. Midforceps and episiotomy. Pressure on admission 100/62, after delivery 98/68. Placenta expressed after thirty-five minutes incarceration by cervix (removal spontaneous). No morbidity. Uterus six fingers above symphysis after delivery, and two fingers above on discharge. Slight pain (cramps) first day. Spotting after third day. Measured blood loss 200 c.c., probably a result of retained placenta.

CASE No. 82.—S. S., aged 34 years, para viii. Spontaneous delivery. Blood pressure on admission 130/92, after delivery 110/70. Retained, adherent placenta with manual removal. Uterus six fingers above symphysis after delivery, and two and one-half fingers on discharge. No morbidity. Spotting after third day. Slight cramps during first two days. Measured blood loss 100 c.c.

Blood Loss Over 450 Cubic Centimeters

CASE No. 4.—A. S., aged 31 years, para ii. Outlet forceps and episiotomy. Blood pressure 124/60 to 118/64. Membranes ruptured mechanically when fully dilated. Uterus atonic after five minutes at the end of the third stage, and second ampule of Methergine was given intramuscularly, followed by firm contraction with massage. No morbidity. Slight cramps on first day. Placenta delivered in three minutes. No flow on tenth day. Uterus six fingers above symphysis after delivery, and three fingers above on discharge. Blood loss 500 c.c. The reason for this amount of bleeding is obscure.

CASE No. 15.—A. M., aged 26 years, para iv. Blood pressure 112/78 to 120/82. Outlet forceps, no episiotomy. Gush of blood with birth of head. Several clots after expression of placenta in two minutes, and second ampule of Methergine was given intramuscularly. No morbidity. Uterus six fingers above symphysis after delivery and one and one-half fingers above on discharge. Cramps on first day. Scant spotting on tenth day. Blood loss measured 500 cubic centimeters.

CASE No. 59.—J. R., aged 24 years, para ii (Dr. M.F.G.). Outlet forceps, left episiotomy. Blood pressure 122/78. Placenta expressed in three minutes. No morbidity. No cramps. Very slight flow on discharge. Measured blood loss 500 c.c. probably due to bleeding vessel in episiotomy.

CASE No. 62.—E. M. L., aged 32 years, para iii (Dr. M.F.G.). Spontaneous delivery. Placenta expressed in four minutes. Two ampules Methergine given intravenously. Slight cramps first two days. No morbidity. No flow after third day. Uterus six fingers above symphysis after delivery, and three above on discharge. Measured blood loss 800 c.c., due in part to laceration through scar tissue.

Postpartum Pain and Lochia

About one-half the patients, more especially the multiparas, complained of slight cramps on the first postpartum day. These cramps started about fifteen to twenty minutes after receiving their first Methergine tablet, and lasted from one-half to two hours. No one complained of afterpains after the second day. Generally, postpartum pain was much less, and the uterus was less tender than when other oxytocics were used. Each day the size of the contracted uterus could be felt at a lower level, so that by the eighth postpartum day it could be palpated at between one to two fingerbreadths above the symphysis.

To date, there have been no postpartum hemorrhages in this series, nor has any woman had a "gush of blood" on getting out of bed. Eleven cases, or 5 per cent, had an elevation of temperature of 99.4° F. or more for two consecutive days. These could be further corrected if we take into consideration that elevation in temperature was connected with full and engorged breasts.

Except for occasional irregular spotting after leaving the hospital, most patients had a thin lochia, after the third or fourth day post partum, devoid of a foul odor. By the time of their six-week check-up the uterus was completely involuted. There was less complaint of low backache; the red cell count showed no more than a mild hypochromic anemia; and their general physical condition was good.

Summary

A series of 180 cases are presented in which a new synthetic drug, Methergine, was used.

The third stage of labor was appreciably shortened.

The blood loss in the third stage was decreased.

The prolonged action of the drug required less medication post partum.

Postpartum bleeding and the amount of the lochia was decreased.

Involution took place sooner and the general condition of the patient was enhanced by its judicious use.

Conclusion

Methergine is a new synthetic oxytocic which seems to be very effective and safe when used in the third stage of labor.

I wish to express my thanks to Sandoz Chemical Works, Inc., who supplied both the ampules and tablets of Methergine used in this series. To the Sisters of Providence and the nurses at the Mercy Hospital, and to Dr. Milton F. Gipstein, I express my gratitude for their cooperation and help in collecting data.

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THE MENSTRUAL CYCLE LENGTH AND VARIABILITY OF YOUNG ADULT WOMEN

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AREY[3] states that almost every aspect of human behavior has been quickly invaded by scientific curiosity, while the most obvious one of individual menstrual variability has been long neglected. Since recent investigations emphasize a definite time relationship between ovulation and menstruation, the length of the normal menstrual cycle has become more than a purely academic problem.[11] To anticipate the time of ovulation in a given individual, experimental results indicate that the typical length and variability of the menstrual cycle is of fundamental importance,[2, 4] particularly when a specific test is to be employed.[6] Menstruation consists of a highly complex physiologic mechanism, but the length and variability of the menstrual cycle may be easily determined. Careful detailed observations on the human menstrual cycle have been made, and the length and variability at certain age levels have been reported,[3, 5, 7, 10, 13-19] but information concerning the pubescent and young adult is scant (Table I). To supplement the accumulated data, the present investigation was undertaken to determine the length and variation of the menstrual cycle in selected groups of late adolescent and young adult women.

TABLE I. COMPILATION OF DATA ON MENSTRUAL CYCLE LENGTH AND VARIABILITY

SOURCE OF DATA	NUMBER OF SUBJECTS	SUBJECT AGE RANGE	MEAN AGE	TOTAL NO. CYCLES	CYCLE RANGE	MEAN LENGTH	STANDARD DEVIATION
Engle and Shelesnyak, 1934*	100	11-15	13.1	3140	7-256	33.9	11.80
Rork and Hellebrandt, 1940	231	—	15.5	1690	8-122	31.9	8.55
Larsen	17	16-20	17.5	130	6-61	28.88	7.11
	26	18-21	19.7	189	21-45	30.05	4.51
	22	18-21	20.2	147	21-47	29.86	4.19
Fluhmann, 1934*	76	18-27	20.4	747	11-144	30.4	11.58
King, 1933*	21	17-35	23.3	161	16-57	29.1	5.46
1926, 1933*	33	17-35	23.8	716	18-53	27.7	3.68
Scipiades, 1935*	50	18-34	24.5	339	20-91	30.2	7.17
Issmer, 1889*	12	19-39	26.8	120	20-40	27.8	2.93
Gunn et al, 1937*	479	13-51	27.3	6000	—	—	—
Latz and Reiner, 1935*	102	20-45	31.0	1113	15-51	28.4	3.27
1937*	100	21-49	31.7	1336	19-101	27.3	3.65

*Arey.[3]

Method

During one academic year each student subject kept a menstrual chart which followed a standardized method of recording data (Table II). The cycle lengths were then calculated, and the data analysed.

TABLE II. MENSTRUAL CYCLE RECORD CHART

CYCLE DAYS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Dates	Menstruation												Ovulation*																
September	*10*	*11*	*12*	*13*	*14*	15	16	17	18	19	20	21	22	*23*	24	25	26	27	28	29	30	1	2	3	4	5	6		
October	*7*	*8*	*9*	*10*	*11*	12	13	14	15	16	17	18	*19*	20	21	22	23	24	25	26	27	28	29	30	31				
November	*1*	*2*	*3*	*4*	*5*	6	7	8	9	10	11	12	13	*14*	15	16	17	18	19	20	21	22	23	24	25	26	27		
November	*28*	*29*	*30*	*1*	*2*	3	4	5	6	7	8	9	*10*	*11*	12	13	14	15	16	17	18	19	20	21	22	23			
December	*24*	*25*	*26*	*27*	*28*	*29*	30	31	1	2	3	4	5	*6*	7	8	9	10	11	12	13	14	15	16	17	18	19		
January	*20*	*21*	*22*	*23*	*24*	*25*	26	27	28	29	30	*31*	*1*	2	3	4	5	6	7	8	9	10	11	12					
February	*13*	*14*	*15*	*16*	*17*	18	19	20	21	22	23	24	25	26	*27*	28	1	2	3	4	5	6	7	8	9	10	11	12	13
March	*14*	*15*	*16*	*17*	*18*	*19*	20	21	22	23	24	*25*	26	27	28	29	30	31	1	2	3	4	5						
April	*6*	*7*	*8*	*9*	*10*	*11*	*12*	13	14	15	16	17	18	*19*	*20*	21	22	23	24	25	26	27	28	29	30	1	2	3	

Subject: E. C.
Year: 1944-45
Birthday: January 18, 1924

Duration of bleeding: 5 to 7 days
Shortest cycle: 23 days
Longest cycle: 29 days
Average length: 26 days
Total number of cycles: 9

*Probable date of ovulation: 12th to 15th day of cycle.

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Results

The subjects of the investigation were seventeen healthy freshmen women averaging 17.47 years of age, and two groups of twenty-six and twenty-two healthy junior women averaging 19.69 and 20.18 years of age.

The results of the freshmen records yielded 130 menstrual cycles ranging in length from 6 to 61 days, with a mean of 28.88 days, and a standard deviation of ±7.11 days. The results of twenty-six junior records yielded 189 cycles ranging from 21 to 45 days in length, with a mean of 30.05 days, and a standard deviation of ±4.51 days. The results of the group of twenty-two juniors yielded 147 cycles which ranged from 21 to 47 days, with a mean of 29.86 days and a standard deviation of ±4.19 days (Table I). The junior data were taken during two different years, with remarkably similar results.

Discussion

It has long been a traditional medical teaching that normally menstruating women do so at regular intervals, demonstrating a 28-day spaced rhythm.[1, 3, 7, 8, 10, 11] This viewpoint is still prevalent in some medical journals and modern textbooks,[3, 7, 10] and it is often the custom to assume the normality of regularity as the basis of clinical questioning for case history purposes.[1, 3]

Long ago it was stated by Fräenkel[9] that the only regularity concerning the menses is their irregularity, and Hartman observed that the strictly regular woman is a *rara avis*.[12] According to Gunn, Jenkin, and Gunn the regular case is either an absolute myth, or is so rare as to be a medical curiosity,[10] and Rossman and Bartelmez state that sufficient data support the conclusion that a recurrent 28-day cycle is an abstraction.[20] The results of this study are in accord with these conclusions. The cycle lengths were markedly variable, falling into three main groups of data: medium length cycles, very short, and unusually long ones. Of the total number of freshmen cycles the medium group comprised the majority of the cycles with lengths ranging from 18 to 41 days; four cycles were very short, 6, 8, 14, and 15 days, and four were unusually long, 55, 56, 57, and 61 days. Of the four individuals who experienced a brief cycle during the course of one academic year, only one individual also had an unusually long cycle. No attempt was made to obtain a diagnosis of the etiology of the extreme deviations from individual norms. However, in the instance of the very short cycle, followed by an unusually long one, this coincided with the initial experience of attending school away from home and undergoing the necessary adjustment to meet these new experiences. Two separate cases of unusually long cycles coincided with midterm examinations, which also suggest emotional stress as a possible disrupting factor.

The freshman cycle length ranged from 6 to 61 days, or a 55-day span, and the junior cycles ranged from 21 to 47 days, or a 26-day span. Thus the junior cycles exhibited a narrower range in length than the freshmen cycles, with the whole junior group falling into the medium cycle length group, skewed toward the high value. The shortest junior cycle was 21 days in length, and there were 6 long cycles in each junior group, 42, 43, 43, 44, 45, 45, and 40, 41, 42, 43, 43, and 47 days, but none to compare with the 61-day freshman cycle.

It has been reported that the menstrual rhythm of pubescent girls averaging 13.1 years of age ranges from 7 to 256 days,[5] or a span of 249 days, and girls averaging 15.5 years range from 8 to 122 days,[19] or a 114-day span (Table I). Thus, with increasing age the pubescent mean cycle length and its variability both tend to decrease.[5, 19] The findings of the present study on the late adolescent are in accord with these conclusions. The freshmen women appear to have a shorter and less variable menstrual cycle than that of younger pubescent girls, and both groups of junior young women exhibit a similar decrease from that of pubescent girls as well as a narrowing of range in length as compared with the freshmen women (Table I). Maturity at the approximate age of 20 years apparently stabilizes cycle length and variability in young women.

Summary and Conclusions

Seventeen freshmen and forty-eight junior young women students, with ages averaging 17.47, 19.69 and 20.18 years, kept menstrual calendar records during one academic year. From these data the length and variability of menstrual cycles were calculated. The investigation yielded 466 menstrual cycles: 130 freshmen cycles ranging from 6 to 61 days in length, and 366 junior cycles ranging from 21 to 47 days in length; the freshman mean cycle length was 28.88 days, and the junior means 29.86 and 30.05 days; the standard deviation for freshmen was ±7.11 and for junior ±4.19 and ±4.51 days.

The results support the following conclusions:

1. The mean cycle length in young adult women is longer than 28 days.

2. There is no significant difference between the mean cycle length of late adolescent and early adult women students.

3. There is an appreciable decrease in the variability of cycle length between late adolescent and early adult women students.

4. Increased maturity apparently exerts a stabilizing effect upon cycle length and variability in young adults.

5. There may be occasional large deviations from individual norms.

6. Arrhythmia of the menstrual cycle of healthy young women students appears to be a normal phenomenon.

The author wishes to thank Esther Charne, Holly Clark, Betty Everett, Margaret Hukill, Ruth Savitsky, Louise Spechalske, and Henrietta Wilkans for assistance with the data.

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A NONSURGICAL METHOD OF THERAPY FOR CHRONIC ENDOCERVICITIS

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CHRONIC cervical infection is the most common lesion seen in gynecologic practice.[1] Fortunately, it is quite amenable to therapy in most instances, and rarely causes much concern to the patient or the doctor. In the treatment of sterility, degrees of cervical infection which would pass unnoticed in the average gynecologic patient may prove an annoying lesion and an efficient barrier to pregnancy. A method which has been found successful in our hands in the eradication of nonspecific endocervical infection is reported.

Materials and Methods

Twenty-five patients are included in this series. All but three were seen with the presenting complaint of sterility; these latter patients were seen because of a chronic discharge of many years' duration. Seventeen of the patients had never been pregnant to their knowledge; eight were parous. All disclaimed knowledge of gonorrheal infection, and the pelvic findings were within normal limits save for the cervical lesion to be described. Two had had therapy to the cervix for over five years, including repeated cauterizations and local therapy. The remainder had histories of short duration or had not noted serious leucorrhea.

The lesion considered in this paper is a definite clinical entity, although not necessarily bacteriologically or even pathologically specific. It is known as chronic endocervicitis and is characterized by the chronic and prolonged discharge of a heavy mucopurulent discharge from the external cervical os. This discharge is composed of mucous which is of high viscosity and opaque character, and, although it is usually at its most profuse stage just prior to and just following the menses, it is necessarily present and annoying throughout the whole cycle. The cervix may be lacerated or virginal, and there may or may not be an accompanying erosion.

Therapy was started only after the patient had been seen on two successive visits, one of which was in the "ovulation phase" of the cycle in order to be sure that the mucus did not become spontaneously clear at this time. At the second visit each patient was instructed to begin therapy three days following the date of onset of the following period. This therapy was as follows: one milligram of stilbestrol was to be taken by mouth daily for the next fifteen consecutive days; at the same time sulfadiazine, one gram three times daily, was to be taken by mouth for three days, and then the dosage was to be reduced to one-half gram three times daily for seven days. This would make a total of 15 mg. of stilbestrol in fifteen days and 19.5 Gm. of sulfadiazine in ten days. The endocervical mucus was re-examined in the "ovulatory phase" of the succeeding cycle, and if the improvement was marked, the stilbestrol was repeated the following month as before with omission of the sulfonamide. If there was no marked improvement, the complete course of stilbestrol and sulfadiazine was

resorted to the following month in the original dosages. Needless to say, if the mucus was water-clear and of low viscosity, therapy was entirely discontinued.

At the first visit the character of the cervical mucus was determined grossly. In almost all instances the mucus was too viscid to be aspirated with a syringe. After therapy, improvement was determined by the gross cloudiness of the layer on a slide over a dark background and by microscopic inspection. Specimens were considered completely satisfactory when the mucus was microscopically free of leucocytes and the viscosity approximated that of saliva.

Results

Results of therapy of twenty-five patients are shown in Table I. In only one case could treatment be considered a complete failure, and here the cervical mucus became of low enough viscosity to aspirate with a syringe, but never clear or significantly reduced in volume. Treatment was continued over twelve months, the prescribed course of therapy being repeated four times. It is of interest that this patient had had this condition for over twelve years, had had a conization of the cervix, several types of cautery applied, and had been advised to have a cervical amputation.

Three patients could not be considered cured, although they improved to the point of clinical disappearance of the mucoid discharge. It was never possible to obtain water-clear mucus of low viscosity, and recurrence of the original condition following cessation of therapy was noted in one of these patients.

Twenty-one of the patients became cured of the cervical discharge so far as could be determined clinically; microscopic visualization of the mucus showed no pus cells. The viscosity was that approximating saliva.

TABLE I. A SUMMARY OF THE RESULTS OF THERAPY OF TWENTY-FIVE PATIENTS WITH CHRONIC ENDOCERVICITIS

	CASES	CURED	IMPROVED	NO CHANGE
Nulliparous	17	14	2	1
Parous	8	7	1	0
Total	25	21	3	1

Discussion

The rationale of this type of therapy is thought to be a combination of estrogenic enhancement of the resistance of the cervical mucosa with stimulation of overgrowth[2] and the antibacterial effect of the sulfonamide drug. Why the body itself has been unable to clear up this low grade infection in most instances is not clear, since all these patients were shown to have been ovulating with reasonable frequency and therefore presumably were maintaining normal estrogen levels.

The effect of ovulation on the amount and viscosity of the cervical mucous has been extensively investigated,[3] and the use of estrogens in lowering viscosity in sterility patients in whom the cervical mucous may be acting as a barrier is considered rational.

The use of sulfonamides locally in the therapy of cervicitis and vaginitis is widespread and the therapeutic advantages are unquestioned.[4] For lesions of the endocervix, little benefit could be expected because of the improbability of contact with the infected gland bases. The systemic use of the chemo-

therapeutic agent invalidates this objection, as in the therapy of low grade urinary tract infections, small dosages seem to be adequate. This is fortunate since one is usually not justified in giving potentially harmful amounts of this drug to ambulatory patients.

Unwonted reactions such as nausea and disturbance of the menstrual cycle were noted in over one-half of the patients, but rarely necessitated discontinuance of therapy.

This series is of necessity small, but the number of absolute failures seems to render it significant. In view of the simplicity and harmlessness of the medication, it would seem to be a logical step to take even in the preparation of the patient who may later need cauterization. If further investigation bears out these results, much cauterization and the resultant inconvenient and even harmful effects of this means of therapy may be obviated.

Sensitivity to either drug employed is obviously a contraindication to this type of therapy.

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SALPINGOMETER AND SELF-RETAINING CANNULA FOR TESTING TUBAL PATENCY

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THE tubal patency test is being performed in many clinics by means of improvised apparatus. Frequently the apparatus is uncommendable, if not actually dangerous. The danger lies in the fact that air is frequently used as the insufflation medium, and is often introduced by means of a rubber bulb or syringe. No safeguards are employed against the sudden and inadvertent introduction of large amounts of air under pressure that exceeds the safe limit.

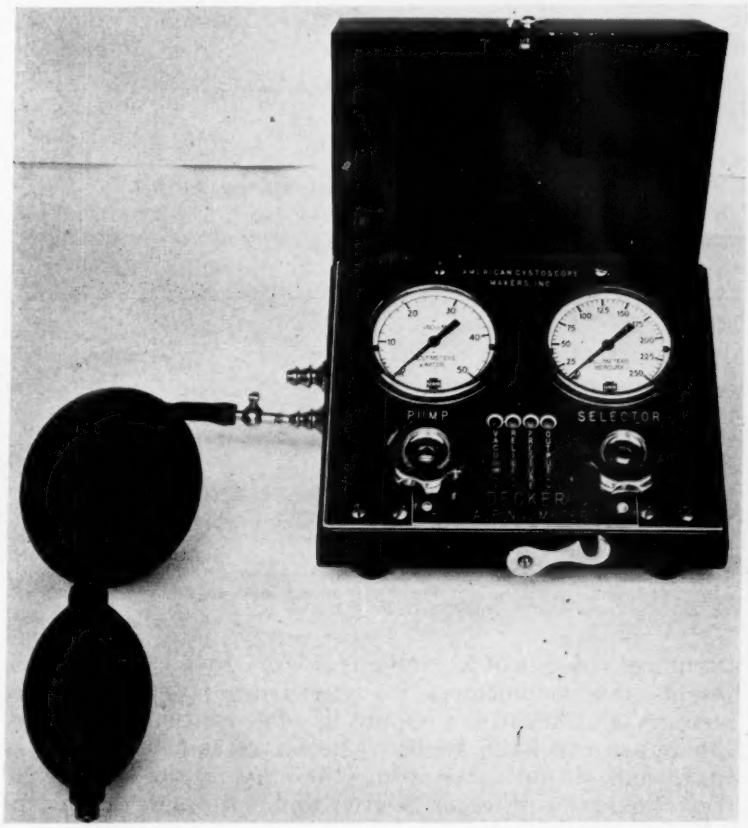

Fig. 1.—The Decker salpingometer with CO_2 container attached to inlet tube.

The introduction of air under pressure into the uterine cavity can result in fatal embolism. Carbon dioxide emboli have never been reported. Air should never be used as a medium for tubal insufflation.

The Rubin test is now widely employed. With the occasional investigator of female infertility, it is frequently the first and only diagnostic procedure employed. There is need for a safe and convenient apparatus.

An apparatus has been devised that permits the safe introduction of small amounts of carbon dioxide by fingertip regulation. The instrument is equipped to measure the intra-abdominal negative pressure in cubic centimeters of water.

Occasionally, tubal patency can be determined without resorting to positive intrauterine pressure. A negative intra-abdominal pressure of 15 to 30 cubic centimeters of water is created by assumption of the knee-chest position. Subphrenic air will occasionally occur when a cervical cannula is introduced in this posture. Such an occurrence is indicative of normal patent, nonspastic tubes. The ability to measure intra-abdominal negative pressure through the cervical cannula is positive proof of tubal patency and, at the same time, avoids the necessity of introducing intra-abdominal gas. Intratubal trauma is avoided, and there is no postexamination distress. The author now uses this procedure as a screening process before applying positive pressure.

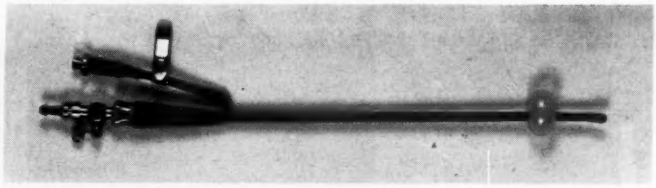

Fig. 2.—Cannula with self-retaining bag inflated.

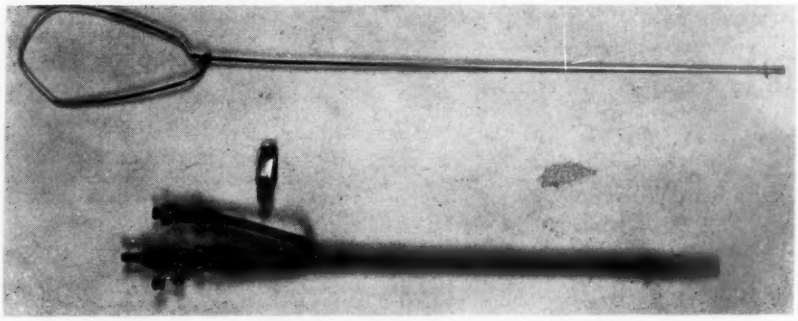

Fig. 3.—*A*, Metal stylet used to introduce the cannula. *B*. The self-retaining cervical cannula with bag deflated. Attachment for bulb or syringe to deflate the bag is shown, also attachment for tubing from the salpingometer.

The instrument consists of a small metal box 7 by 6 by 5½ inches and, when opened, presents two manometers for measuring positive pressure in millimeters of mercury and negative pressure in cubic centimeters of water. Below the meters there are two hand knobs. One serves as a pump and is connected with the intake and output tubes, while the other is the selector to direct the flow of carbon dioxide in different desired routes through the instrument. The output tube is attached to a length of rubber tubing, and the input tube is attached to a bag previously filled with 100 to 300 cubic centimeters of carbon dioxide. When the rubber tubing from the salpingometer is attached to the self-retaining cannula, the carbon dioxide is introduced five cubic centimeters at a time by slowly turning the pump knob in the manner usually employed in winding a watch. The intrauterine pressure attained at all times is indicated in millimeters of mercury on the positive pressure manometer. The author also employs a monaural stethoscope over the lower abdomen to hear the air escape from the tube. With one ear free, it is easier to differentiate sounds caused by intraperitoneal gas and the gas escaping at the cervix.

The principle of the Foley catheter has been adapted to the cervical cannula.* The cannula consists of a catheterlike rubber tube with a small inflatable rubber bag integral with the outer wall of the tube near the tip. The cannula is introduced by means of a stylet which can be molded to any direction of the cervical canal. When the inflatable rubber bag is beyond the internal os, it is inflated with 3 to 5 cubic centimeters of air and the stylet removed. The cannula remains in place when properly introduced and can be manipulated with ease without the use of a tenaculum on the cervix. Inflation of the bag within the canal diminishes its self-retaining property and is more painful. The cannula is particularly useful when it is desired to change the position of the patient to the lateral, prone, or knee-chest.

Method of Examination

The instrument is placed on a table beside the examiner. The carbon dioxide bag is partially filled with gas and attached to the input tube. The length of rubber tubing is attached to the output tube. The stylet is placed within the cannula and it is slipped through the cervix until the bag is beyond the internal os. The bag is then inflated and the stylet removed. The cannula is clamped near the end and the patient changed to the knee-chest position. The rubber tubing is attached to the cannula, and the selector moved to vacuum. The clamp on the cannula is then removed. Small changes in the negative pressure are usually due to a vacuum within the tube. Readings of 10 to 15 cubic centimeters of water are indicative of normal, nonspastic tubes, and further examination is unnecessary. Tests with positive pressure can be made in the dorsal or the knee-chest position.

In the event that negative pressure is not noted, the selector is moved to output (positive pressure) and the pump knob is turned slowly in the manner of winding a watch and the positive pressure noted on the manometer.

Summary

An instrument to test tubal patency has been described that makes use of intra-abdominal negative pressure and positive pressure with a carbon dioxide medium.

A self-retaining, intrauterine cannula employing the Foley catheter principle has been described.

*The American Cystoscope Makers, Inc., New York, who manufacture the Foley catheter, also make the cannula.

A NEW ENDOMETRIAL BIOPSY CURETTE

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THE gynecologist who does any volume of microscopic endometrial studies, and is forced by necessity to use the endometrial curettes now on the market, cannot help but be impressed with the difficulty and awkwardness entailed in their usage.

The more simple the task in obtaining curettings, and the ease with which the specimens can be obtained, the more often the gynecologist will include this valuable adjunct to his armamentarium of diagnostic procedures.

The endometrial curettes now on the market include the standard type loop uterine curette and the biopsy suction curette with its various modifications.

The loop curette is not satisfactory for office biopsies due to its size and the difficulty in evacuating the curettings from the uterus when seeking only small amounts of tissue.

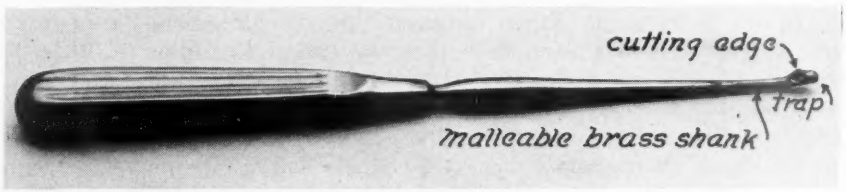

Fig. 1.

The suction curette, although small, has the disadvantage of being of rigid construction and not adaptable to all variations in directional contours of the endometrial cavity. Likewise, whether the suction feature of the curette is used or not, it requires the curettings to sweep up into the hollow shank of the handle, which is a direction they follow with difficulty unless suction is applied.

The endometrial biopsy curette here described has in my hands eliminated the undesirable features of the suction curette. Because of its simplicity, and the ease with which specimens can be obtained, it appears to be superior to other curettes.

The curette consists of a head which contains a steel cutting edge similar to the sharp loop curette. Just below and distal to this cutting edge is a hollow trap to retain the detached endometrium. The cutting head has an over-all transverse diameter of $\frac{3}{16}$ inch, and the trap inside measures $\frac{3}{16}$ inch by $\frac{3}{16}$ inch. This gives a fairly satisfactory sized piece of tissue with only one sweep of the instrument. The distal end of the shaft adjacent to the cutting head is of soft malleable brass which can be molded to fit any type of contour. This ability to shape the shaft adds greatly to its efficiency. Likewise, the larger four-sided handle makes the ease of handling the instrument much superior to that of the suction curette.

Fig. 1 illustrates the cutting head and trap of the curette.

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GYNOGRAPHICS

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GYNOGRAPHICS may be defined as "symbolism in obstetrics and gynecology."

The use of symbols is an old custom in the history book of mankind. Thus, the astronomers, the botanists, and the chemists have long availed themselves of a system of signs[1] for the purposes of brevity and lucidity. Physicists have long used the symbol "M" for mass. Mathematicians have for

Fig. 1. Key

centuries used such symbols as "π" and "πr^2" with notable success. History-taking in gynecology and obstetrics might similarly gain by the use of such a system. This is not at all entirely new to gynobtrics.* Thus the Roman symbols for Mars and Venus have long been used for denoting the male (♂) and the female (♀).

The important gynecologic and obstetric signs and symptoms can be broken down to a relatively small number, and translated into symbol form (Fig. 1). These symbols can be projected in sequence on a life graph, which may aptly be called a "vita-gynograph."

"Gynographics" have the following advantages: (a) speed of recording; (b) speed of interpretation; (c) conciseness, clarity, and comprehensiveness; (d) signs and symptoms in sequence at a glance; (e) universal language.

The author wishes to thank Faith Hope Kahn, R.N., for her painstaking assistance in the experimental phases of the translation of many actual case histories into "vita-gynograph" form.

Reference

1. Koch, Rudolph: The Book of Signs, London, 1930, First Edition Club.

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*"Gynobtric": pertaining to gynecology and obstetrics. ("gynobtrician": one who practices gynecology and obstetrics.)

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